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CURRENT RESEARCH ON ANTIBIOTICS

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Antibiotics are undoubtedly in the forefront of present day medicine, but in many respects theoretical understanding has not kept pace with practical advances. With the ever increasing number of new antibiotics and the enormous literature dealing with the subject, the confusion has become worse instead of less. Since the treatment of infectious diseases depends in large measure on the intelligent application of the knowledge we have gained regarding the clinical behavior of the antibiotics, and since these new drugs, marvelous as they undoubtedly are, have definite limitations, it becomes the duty of the physician to keep himself informed of the progress of knowledge concerning these agents. Advances in the clinical utilization of older antibiotics as well as evaluation of more recently discovered drugs will be discussed. In addition, wherever possible, reference will be made to progress in the understanding of the biologic mechanisms to which various antibiotics owe their effectiveness. In this connection, untoward side effects of antibiotic therapy are of both practical and theoretical significance. Finally, some recently reported properties of commonly used antibiotics will be discussed which are apparently not directly related to their antimicrobial activity.

There will be no attempt at complete coverage in any one of these fields; this would be manifestly impossible in the space available. The terms chemotherapeutic agent, "drug," or antibiotic are used interchangeably. The original distinctions between these terms is today of academic interest only, as more and more "naturally occurring substances" are being prepared by chemical synthesis.

PENICILLIN

Penicillin still is the safest, most versatile and generally satisfactory antibiotic yet produced. The story of its discovery and development is already as well known as that of Ehrlich's famous "magic bullet," Salvarsan. Its mode of action has been extensively studied. George and Pandalai[1] claim that penicillin exerts its powerful bactericidal effect by interfering with the nucleic acid metabolism of gram-positive bacteria. Gale[2] showed that *Staphylococci* require an external source of glutamic acid and that this assimilatory mechanism is blocked in the presence of sufficient penicillin. These two views could be reconciled by assuming that glutamic acid becomes a constituent of nucleoprotein.

The therapeutic applications of the drug have been well delineated in the past few years. In general, it is most effective against infections caused by gram-positive cocci, *Neisseriae*, *B. anthracis*, Spirochaetes, and, to a limited extent, certain of the Actinomycetes, and the larger viruses of the Lymphogranuloma-venereum-Psittacosis-Ornithosis group.

Certain bacteria, particularly the *Staphylococci* and *Neisseriae*, possess an inherent tendency to become resistant to increasingly larger concentrations of penicillin. With the ever widening indis-

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criminate use of the drug, this phenomenon becomes more apparent. Fortunately, this is not yet as serious a clinical problem as it was with the sulfonamides, because penicillin resistance is usually not of a high degree, and the doses commonly used are far in excess of the minimal inhibitory concentrations. Nevertheless, the principle that antibiotics must be given in full doses and promptly, is still valid for this reason.

Some organisms which are naturally penicillin resistant, particularly the gram-negative bacilli, are active producers of penicillinase, an enzyme which is capable of rapidly inactivating penicillin and thus render it impotent against otherwise susceptible species which may be present in mixed infections. It is well to keep this fact in mind when treating infections caused by a mixture of bacteria with penicillin alone, since associated coliform bacilli, for example, may produce enough of the enzyme to inactivate the drug and thus reduce it below the therapeutic level.

A currently debated problem concerns the optimal administration of penicillin; that is, how maximal therapeutic effects can be attained. It was thought for some time that a continuous high plateau of the drug level was necessary for the greatest antibiotic effect. Gerber[3], Jawetz[4] and others claim that peaks of high levels alternating with low ones are preferable and more practicable. Doses of 100,000 to 300,000 Oxford units given twice daily intramuscularly are adequate in most infections caused by sensitive or moderately susceptible organisms. The amount required also depends, to a large measure, on the extent of the infection and the degree of tissue break-down at the start of the treatment. In such diseases as subacute bacterial endocarditis, where the invading organism may be protected by impermeable layers of tissue, larger doses are usually required. It has been established that the lethal action of penicillin continues for some time after its concentration in the blood falls below detectable levels. Tissue levels were shown by Schachter[5] to be higher and to persist longer than serum levels; this supports the hypothesis that a consistently high blood level is not necessarily essential for the best clinical effect, and therefore injections may be widely spaced with safety.

Almost every conceivable form of the agent is available—troches, oral tablets, ointments, vaginal and rectal suppositories, aerosols, forms for ion transfer, and for intra-arterial injection by "hypospray". None of these can compare with intramuscular administration for safety, efficiency, and height of level attained, but they have their uses in special circumstances. Of the many forms available for intramuscular injection, the so-called "depot" penicillin is a new preparation that seems to be eminently satisfactory. It is a mixture of water-soluble potassium salt of penicillin with an insoluble procaine salt. A high initial level is obtained with this mixture, due to the rapidly absorbed potassium salt, and maintenance of the prolonged level is due to the slow absorption from the procaine depot. The allergenic potentialities and unpleasant reactions caused by oil and beeswax preparations are obviated by the more physiologic aqueous vehicle of this new preparation.

Numerous studies were carried out on methods to increase the effective blood level of penicillin by blocking part of the renal tubular mechanism. Para-aminohippuric acid, benzoic acid, diodrast, carinamide, and many others have been tried with some success. According to the current consensus of opinion among clinicians, these methods are laborious, expensive and unnecessary.

Primary toxicity of penicillin is practically unknown. However, untoward reactions, allergic in nature, seem to occur with increasing frequency. This is not surprising in view of the ever-widening use of the drug and the greater likelihood of a person who has become sensitized to be subsequently re-exposed to penicillin. Fortunately, severe allergic reactions, such as were reported by Walley[6], are exceptional. As a rule, these reactions are not serious, and almost invariably they are transitory. Individuals with superficial fungus infections more often display an allergic flare-up, particularly following local therapy.

A somewhat different situation prevails in relation to another manifestation of hypersensitivity, namely, the so-called Jarisch-Herxheimer reaction in syphilis. In its mildest form, this reaction is febrile, but it may be also expressed in the form of severe exacerbations of clinical symptoms and may even result in sudden death. Such reactions have been known to occur soon after initiation of antisyphilitic treatment of any kind, and have been thoroughly studied in arsenotherapy. Evidence points to perifocal inflammation of syphilitic lesions, comparable to hypersensitive reactions occurring in tuberculosis, as the causal factor in the Herxheimer reaction. Hence such reactions may be unavoidable in any type of effective antisyphilitic treatment. Extensive studies on the occurrence of Jarisch-Herxheimer reactions on penicillin-treated syphilitics have been reported[7]. For the most part, reactions occurring in about 40 per cent of patients with early syphilis were mild, febrile ones. However, two fatalities have been recorded, one in a case of central nervous syphilis, and another of cardiovascular syphilis[8].

The increased coagulability of the blood which has been alleged to occur as a result of penicillin therapy, has not been confirmed by other workers[9]. Similarly, aureomycin administration failed to shorten the coagulation time in humans[10].

A side effect of antibiotics in general which should be kept in mind in clinical practice, is based on their bacteriostatic effects on the intestinal flora. Pathogens as well as harmless saprophytes may be thus affected. Suppression of symbiotic organisms may even result in detrimental phenomena, such as impaired utilization of food or lessened production of vitamins. For instance, such a mechanism was assumed to have been the cause of deficiency of nicotinamide, which was observed following oral administration of penicillin[11].

While penicillin continues to be the most useful antibiotic and probably will retain this position for some time to come, it is not a panacea. The occurrence of naturally resistant strains of bacteria, the development *in vivo* of resistance during therapy, the occurrence of penicillinase producers, occasional individual idiosyncrasy to the drug, and its failure to control a wide group of infections, particularly those caused by gram-negative bacilli and Mycobacteria, by necessity assign an important position to other antibiotics.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

In a sense, the action of streptomycin is complementary to that of penicillin; that is, most pathogenic bacteria are affected either by one or the other. Thus, it may appear that these two substances alone should be sufficient to control most bacterial infections. Unfortunately, such is far from being true. Streptomycin cannot compare with penicillin as a generally satisfactory chemotherapeutic agent. Outside of some infections caused by penicillin-resistant organisms, certain gram-negative bacilli and Mycobacteria, the net result of therapy is invariably less striking than with penicillin. This may be due to fundamental differences in their mode of action. Streptomycin is thought to exert its effect by inhibiting an enzyme which is involved in the carbohydrate metabolism of the cell. It is active against young and old forms, in contrast to penicillin, which is active only against growing cells.

The drug is rapidly absorbed, and plasma concentrations reach a peak one hour following a single intramuscular injection. The rate of fall is directly proportional to the dose per unit of body weight. Hence it is necessary to maintain relatively high concentrations in the blood stream. Little, however, is to be gained by too frequent injections of the drug; intervals of at least 6-8 hours, or even longer, are usually satisfactory.

Organisms tend to vary in their susceptibility to streptomycin, not only among different species, but among different strains of the same species. Some bacteria tend to become resistant to the drug in a phenomenal fashion, often overnight. This strong tendency of bacteria to become resistant makes brisk and intensive therapy with this drug essential. It is also extremely important

to test the *in vitro* sensitivity of bacteria isolated from the patient, not only before treatment, but during and after therapy as well. Should a patient be treated with an inadequate amount of streptomycin initially, thus permitting the development of "drug-fastness", even greatly increased doses may fail to control the infection.

Excretion is almost entirely through the kidney. It is considerably slower than with penicillin, and hence the question of depot injections has aroused little interest. Since the substance is bacteriostatic, in contrast to penicillin, which is bactericidal, it has little value locally. For this reason, as well as in view of high local allergenic properties, it is little used in this manner. Orally, it was thought to be of some value as an adjunct in clearing the bowel of potential pathogens preceding major abdominal surgery, but the sulfonamides and the newer orally effective antibiotics seem much better suited for this purpose.

The most important limitation to the use of streptomycin is the high incidence of dermatoses, local and renal irritation, histamine-like reactions, and most serious of all, persistent or transitory neurotoxicity chiefly manifested by involvement of the eighth cranial nerve. Because of the serious limitations, various analogues have been prepared and studied. One of these, dihydrostreptomycin, which is prepared by catalytic hydrogenation of the parent compound, was for a time considered to be the answer to the objections raised to streptomycin. The two drugs appear to be identical qualitatively, except for their antigenicity, and quantitatively except for the difference in toxicity. The dihydro-derivative possesses no advantages over streptomycin in the control of infections caused by drug-resistant strains, nor is it completely devoid of neurotoxicity *per se*. It was even reported to have the potentialities of causing a peculiar explosive type of vestibular damage under certain conditions[12]. Thus, while dihydrostreptomycin has an equivalent therapeutic efficiency and a somewhat lower degree of neurotoxicity than does streptomycin, it does not appear to be the solution to the deficiencies of the latter.

Increasing interest is given at present to the combined use of streptomycin together with other antimicrobial agents. In theory, the effect of such combined therapy might be detectable in two distinct fashions: first, the emergence of drug-resistant strains may be arrested, and secondly, the course of infection might be altered to an extent not observed when either one of the antibiotics is used alone. One of the earliest and best demonstrations of the value of such combinations was the use of streptomycin and sulfadiazine in brucellosis. Other widely used combinations are streptomycin and penicillin in the treatment of subacute bacterial endocarditis caused by *Enterococci;* streptomycin and penicillin as an aerosol in the therapy of bacterial allergy, bronchiectasis and bronchial asthma; and the combination of streptomycin with para-aminosalicylic acid, or one of the sulfones such as promizole, in the treatment of tuberculosis. In the last instance it has been shown that this type of combined therapy definitely delays the emergence of streptomycin-resistant tubercle bacilli.

Streptomycin is most widely used for the treatment of tularemia, Friedlander's pneumonia, infections of the genito-urinary tract caused by susceptible strains of *E. coli, A. aerogenes, Proteus* and *Pseudomonas,* in *H. influenzae* meningitis, and tuberculosis. Newer antibiotics which are considerably safer and more effctive than streptomycin are now narrowing the field of usefulness of this agent, so that its chief value clearly lies in the therapy of certain types of tuberculosis. But even in this disease its limitations are apparent. The previously mentioned neurotoxicity, the emergence of drug-resistant strains of tubercle bacilli and its somewhat general lack of potency so severely limit the value of the drug in this disease that most clinicians will employ it only when no other form of therapy offers a reasonably good prognosis[13].

NEOMYCIN

The discoverers of streptomycin, Waksman and his group, have been ac-

tively seeking new antibiotics which would be less toxic, less prone to lead to development of drug-resistant strains, and which would be more potent. Their search has culminated in the isolation, from a strain of *Streptomyces fradiae,* of neomycin, announced in March of 1949[14]. It was found to have a broad spectrum of activity against various gram-negative and gram-positive bacteria. It was also highly active against experimental infection of animals with *Mycobacterium tuberculosis.* Increase in resistance of bacteria to neomycin was established *in vivo* or *in vitro,* only with great difficulty. A significant finding was that it was as active against streptomycin-resistant strains as it was against sensitive ones. One strain of *M. tuberculosis,* resistant to 400 units of streptomycin, was destroyed by neomycin at a concentration of 0.2 U/cc.

The toxic level for a 18-20 gms. mouse is between 2000 and 5000 U. and the ratio between toxicity and therapeutic activity is between 20 and 50, which is considered to be a wide margin of safety provided that such results can be duplicated in humans.

Although the drug is still new and in the experimental stage, all indications thus far point to its great potentialities. Some success has been achieved in controlling *Salmonella,* stubborn *Pseudomonas aeruginosa,* and *E. coli* infections that have failed to respond to other antibiotics. Orally, it has been tried with promising results in amebiasis. Extensive research is under way to evaluate its usefulness in tuberculosis, and preliminary reports indicate that this agent may succeed in obviating most of the dangers and disadvantages of streptomycin.

CHLORAMPHENICOL (CHLOROMYCETIN)

Chloramphenicol, or "chloromycetin", as it is known commercially, was originally isolated from culture filtrates of the mold *Streptomyces venezuelae* by Burkholder[15] and independently by others. It was soon afterwards successfully chemically identified and synthesized by a research group of the Parke-Davis Co. The pharmacologic properties of the material produced by fermentation and of that derived from chemical synthesis are identical in every respect. The successful laboratory synthesis of this compound is a step of far-reaching significance. It enabled investigators to procure laboratory and clinical data based upon the activity of the pure substance, as standardized by weight.

Initial studies revealed that its antibiotic spectrum was broad, particularly so against the gram-negative bacilli and the Rickettsia. It is at least two to sixteen times as active against these organisms as is streptomycin, and seven to sixteen times as compared with penicillin. It showed little *in vitro* activity against viruses, Mycobacteria, Protozoa or Spirochaetes, with the one exception of *Borellia recurrentis.*

The drug is ordinarily given orally. In infants or where the unpleasant taste is objectionable, it can be given *per rectum,* in capsules of 125-250 mg., which dosage is sufficient for the drug to appear in the blood in therapeutic concentrations. Maximum blood levels occur within two to six hours, urinary levels between 2 and 12 hours. It disappears from the blood within 12-16 hours after oral administration, hence intervals between doses must never be longer than 8 hours. A total dose of 10-15 Gm. seems to be adequate in the majority of cases.

The toxicity of the drug is slight and large amounts are well tolerated. As much as 60 Gm. have been given without untoward effects. There is no cumulative toxic effect on kidney function or on hematopoiesis. Some experiments even seem to indicate that there might be a synergistic effect of chloramphenicol with penicillin or streptomycin. It passes through the placental barrier readily, and is present in the cord blood in a centration 50-70 per cent of that found in the maternal circulation. It also readily passes the blood-brain barrier, and after oral administration it was found in the spinal fluid in concentrations 30-50 per cent of that found in the blood[16].

The excellent effect on Rickettsia *in vitro* stimulated clinical trial of the drug against tsutsugamushi fever. The American Army team testing the drug in Ma-

laya found it to be effective also against typhoid to an extent that no other substance had as yet shown[17]. Soon after that, patients with undulant fever in both the chronic and the acute phases were successfully treated. It has also shown value in treatment of Q fever, typhus, pneumonia caused by *D. pneumoniae* or Friedlander's bacillus, and in gram-negative urinary tract infections. Since chloramphenicol is effective against the gonococcus but not as active as penicillin against *Treponema pallidum*, and since a drug capable of controlling gonorrhea without masking concurrent syphilitic infection is desirable, clinical trial of this antibiotic for this purpose is indicated[18].

In summary, chloramphenicol is an orally effective, non-toxic drug which at this time appears to be particularly useful in treating most Rickettsial infections, brucellosis, typhoid fever, and acute and chronic infections of the urinary tract caused by sensitive organisms. Further fields of application await additional studies on the usefulness of the drug.

AUREOMYCIN

This antibiotic, which owes its name to its golden color, was isolated by a research group in the Lederle Laboratories from a recently characterized mold, *Streptomyces aureofaciens*. Preliminary studies soon showed that it had an unusually wide range of therapeutic activity against a variety of bacterial, Rickettsial and viral pathogens. Thus it is the first antibiotic to display any efficacy in controlling the more elusive microorganisms as well as bacteria.

Attempts to demonstrate an aureomycin-inhibiting substance, comparable to penicillinase, have failed thus far. Aureomycin-resistant strains of bacteria are seldom encountered, and it appears difficult to produce such resistance *in vitro*. Hence one may conclude that the development of resistence to this antibiotic *in vivo* should not be an important problem. No evidence of cross-resistance with other antibiotics exists.

Toxicity is very low, the most serious effects being occasional mild and transitory nausea, vomiting and diarrhea. No drug idiosyncrasies, or blood dyscrasias, attributable to this antibiotic have as yet been reported, although individuals might become allergic to it in the same fashion as they do to other antibiotics. The toxic level in mice following subcutaneous injection is 4000-5000 mg/kg., and the LD_{50} for intravenous injections is between 50-100 mg./kg. of body weight.

The mode of action is still unsolved. Loomis[19] postulated that aureomycin specifically depresses phosphorylation without inhibiting respiration, possibly in a fashion similar to atabrine and gramicidin. It is not inconceivable that actively multiplying microorganisms might be especially sensitive to even minor reductions of phosphate bond energy and in this way could be injured without concurrent damage to mature host cells, which are not dividing as rapidly and hence are less sensitive.

The drug is ordinarily given by mouth. Intramuscular injection produces a moderate amount of local pain and irritation which can be somewhat alleviated by the addition of a small amount of procaine hydrochloride. Following intravenous injection, 30-40 per cent of patients develop irritation of the perivascular tissue at the site of injection. This route is used in patients who are gravely ill, who are unable to take medication by mouth, or whose absorption from the gastro-intestinal tract is impaired, and where an instantaneously high blood level is essential. Solutions for ophthalmic administration, ointments and troches are also available.

Aureomycin in its present form, loses activity rapidly when kept in solution at physiological pH and temperature range. Laboratory studies must be interpreted in the light of this undesirable characteristic. For this reason, or others as yet unexplained, the drug sometimes appears to be more effective in controlling an infection *in vivo*, than *in vitro* studies of the sensitivity of the invading microorganism may indicate.

It is evidently excreted in the glomerular filtrate, the major portion being excreted within twelve hours after oral administration. The largest part of an intravenous dose is disposed of by methods other than by urinary excretion.

This accounts for the necessity of giving treatment in doses spaced at four to six hour intervals. Sanders *et al.*[20] studied the effect of carinamide in maintaining the blood level following intravenous administration. While the effect was definite, this method does not appear to have any practical clinical value.

In spite of the recent date of discovery and the absence of clearly defined indications, aureomycin appears to be one of the most generally useful and versatile antibiotics, as demonstrated by its broad range of activity. Unfortunately, many of the preliminary glowing accounts of its worth, that were based on a small number of cases, have not been confirmed in more extensive trials. Nor can successful tests *in vitro* against certain viruses be necessarily expected to be followed by consistently excellent clinical results. Nevertheless, it appears to be highly effective in the treatment of generalized peritonitis, infections caused by the Lymphogranuloma-venereum-Psittacosis group of viruses, in brucellosis, tularemia, leptospirosis (Weil's disease) and in infections of the urinary tract caused by *Streptococcus fecalis,* penicillin-resistant gram-positive cocci or *Neisseria.* It is useful in surgical procedures for prevention of infection. Strax and Wright[21] reported excellent results in the pre-operative preparation of patients. undergoing abdominal surgery with aureomycin and a more effctive reduction in the intestinal flora than that achieved with the insoluble sulfonamides or streptomycin. It is also effective in primary atypical pneumonia and in many Rickettsial infections. The reports of its value in viral diseases such as influenza, lymphocytic chloriomeningitis, etc., must be considered with skepticism, since in most of these reports the possible involvement of causative agents other than these viruses could not be ruled out. Beneficial effects in typhoid fever, *Shigella* and *Salmonella* infections, coccidioidomycosis, infectious mononucleosis and *Pseudomonas* and *Proteus* infections are doubtful or insignificant according to the latest reports. A purely palliative role, though not less remarkable, of aureomycin was recently demonstrated in the treatment of fibrocystic disease of the pancreas; the severe pulmonary changes which frequently cause death of infants with this disease could be prevented by early initiation of antibiotic therapy[22].

A few interesting observations have been reported within the last year, which indicate that aureomycin and possibly other antibiotics, possess hitherto unknown biologic properties. Thus, preliminary animal experiments suggest that aureomycin may be useful in preventing radiation sickness in cancer patients treated with heavy doses of X-ray. It does not, however, prevent the hemorrhagic tendency due to radiation damage[23].

Another new approach was opened by investigators who found that aureomycin represents a potent animal growth factor[24]. Continued work will be required for elucidation of the full significance of this property. On the other hand, French workers[25] noted degenerative changes in tissue cultures of chick embryos to which aureomycin or chloramphenicol had been added. If this "histiolytic" activity of some antibiotics will be confirmed in further studies, it will be well to heed an editorial warning[26] that clinical use of antibiotics must take into consideration these new potentialities, particularly in conditions of tissue repair.

TERRAMYCIN

This newest of the antibiotics is derived from still another species of Streptomyces, *S. rimosus.* The first report of its isolation appeared early in 1950[27]. It was evident from this report that the substance possessed considerable antimicrobial activity and a low degree of toxicity in laboratory animals.

In vitro sensitivities showed the same range of activity as aureomycin, and effectiveness towards the same group of bacterial, Rickettsial and viral pathogens. *Brucella* is more sensitive to terramycin than to aureomycin. *P. aeruginosa* and *Proteus* are resistant to this antibiotic as they are to most others.

The drug is given orally in doses of 1 Gm. every six hours. The maximum tolerable daily dose is 100 mg./kg. body

weight. Untoward reactions are similar to those encountered with aureomycin but occur less frequently. Giving the drug with cold milk, reduces the incidence of nausea and vomiting. Large amounts are not absorbed and are excreted in the feces; consequently the fecal flora is considerably altered.

Its clinical use has so far been too limited to permit at this time any conclusions as to its efficacy. From the data already accumulated, it seems to possess attributes so strikingly parallel to those of aureomycin that its position in the therapeutic armamentarium should be evaluated in that light.

BACITRACIN

Bacitracin is a polypeptide antibiotic which was discovered in 1943, and announced two years later, by Meleney and Johnson[28]. It was extracted from a filtrate of a strain of *Bacillus subtilis* which was isolated from a wound infection of a child named Tracey, and it was named in her honor. It is neutral, soluble in water, saline and dilute mineral acids, and is heat-stable.

It has a powerful antibiotic action with a wide antibacterial spectrum. It is highly active against most gram-positive organisms, particularly the *Clostridia* and anaerobic cocci, *Actinomyces bovis, Treponema pallidum* (Reiter strain), *Hemophilus influenzae,* and the Diphtheria bacillus. Naturally resistant strains are seldom encountered, and susceptible organisms can be made resistant *in vitro* only with difficulty. Attempts to discover a bacitracinase, an inhibitory enzyme similar to penicillinase, have thus far been unsuccessful.

At first, the main interest in the drug centered about its use in surgical infections, since the mentioned properties appeared very promising for this purpose. Unfortunately, the first commercial lots prepared by the surface growth method displayed some alarming nephrotoxicity on parenteral injection; subsequent lots made by another manufacturer by the deep tank process exhibited greatly reduced toxicity. The renal irritation appears to be due to impurities in the preparation rather than in the bacitracin itself. Studies revealed that those lots which had an LD_{50} of 500 or above for mice of 20 Gm. were safe for parenteral injection. It appears that newer supplies which can meet this specification will soon be approved by the Food and Drug Administration for use by such a route. Nevertheless, the nephrotoxic activity of bacitracin must be closely watched. Recent clinical investigations revealed that therapeutic doses of bacitracin were always followed by proteinuria and appearance of renal tubular epithelium in the urinary sediment. Sometimes post-absorptive glycosuria took place, and renal function tests indicated that in most instances both glomerular and tubular functions were depressed[29].

The available preparations are administered orally, topically, or by direct infiltration into the lesion. It has what is probably the lowest index of allergenicity of any of the widely used antibiotics. Local sensitivity has virtually never been noted. In concentrations up to 1000 units per cc., it is not locally toxic or irritating, nor is it inhibited by pus, plasma, tissue breakdown products or organisms that produce penicillinase, a distinct advantage over other locally applied antibiotics.

The drug is widely used in surgical infections, especially in penicillin-resistant infections, and those caused by a mixed group of organisms. Derzavis and Rice[30] state that in their experience it is the most effective single drug available for treating superficial streptodermas, staphylodermas and impetigo contagiosa. Bacitracin is thought to be a drug of choice in ophthalmic infections caused by gram-positive organisms. Most[31] and others report success in treating amebiasis with oral bacitracin in total doses ranging from 40,000 to 160,000 units a day for a period of twenty days, with excellent clinical and parasitologic results.

It has been injected intrathecally in neurologic infections without signs of meningeal irritation. Meleney and Johnson[32] report that, in dogs, powdered bacitracin could be applied directly to the brain surface, injected into the ventricle, or directly into brain tissue, in concentrations as high as 1000 units per cc. without causing any evidence of irrita-

tion in any case. Eagle and Fleischman[33] noted a striking synergistic effect between bacitracin and penicillin in *Treponema pallidum* infections in rabbits. Bachman[34] found this effect also with respect to numerous strains of penicillin-resistant streptococci isolated from cases of subacute bacterial endocarditis. This synergism was also found in this laboratory with penicillin-resistant cocci isolated from the human vaginal tract[35]. This phenomenon may have practical applications; simultaneous administration of a mixture of penicillin and bacitracin in subcurative doses may be able to control infections which would be uncontrollable with either drug alone in moderate doses.

Bacitracin appears to have an ever widening range of usefulness, particularly in the treatment of diseases caused by bacitracin-susceptible organisms, in mixed infections, and pyogenic cutaneous and ocular infections. Many more strains of organisms are resistant to penicillin than to bacitracin, and the wider margin of safety of the latter makes it preferable to penicillin in these conditions.

THE POLYMYXINS

Polymyxin is a generic name for a group of closely related antibiotics elaborated by *Bacillus polymyxa*, an aerobic spore-forming rod occurring in the soil. Chemically, the substances are polypeptides which form water-soluble salts with numerous acids. The terminology is confusing, since several very similar substances were discovered at the same time, but polymyxin B or "Aerosporin", as the British term it, is the only one of any general clinical interest. The various polymyxins differ mostly in their possession of the amino acids leucine, serine and phenylalanine. Polymyxins differ in their effects on bacteria neither qualitatively nor quantitatively[36] but they do differ in their toxicities.

Polymyxin is unique in its remarkable specificity against gram-negative bacilli. The drug is given by intramuscular or intravenous injection only; oral administration requires about 4 times as high a dose as does intramuscular in order to obtain an equivalent blood level. When the dosage exceeds 4 mg. per kg. of body weight, nephrotoxic and neurotoxic phenomena appear. Malaise, elevated temperature and anorexia also occur frequently.

The drug has been used in the treatment of pertussis, *H. influenzae*, meningitis, and urinary tract infections caused by bacteria of the Coli-Aerogenes group and *Pseudomonas aeruginosa*. Most members of the *Proteus* group are resistant. Its use at this time appears to be limited to those cases where the distinct danger of toxicity is outweighed by its effectiveness in infections where other types of therapy have failed. In general, however, the drug is not suitable for general clinical use in the form available at present[37].

OTHER ANTIBIOTICS

The dramatic therapeutic success of certain antibiotics, notably those derived from *Penicillium* and *Streptomyces*, have spurred the search among other micro-organisms, higher plants and animals, and almost every other conceivable source, for additional substances possessing antibacterial, antiviral, and antifungal properties. Within the past few years, literally hundreds of agents have been tested. Very few of these have proven to be safe for human administration. The following enumerates a few which have some general interest:

1. Tyrothricin. This is the oldest antibiotic in current use, having been isolated by Dubos in 1939. It is a mixture of two active substances, gramicidin and tyrocidin. It can be used locally only, since it is hemolytic and toxic. At one time it was of some value in superficial pyogenic infections, but now it has largely been replaced by newer and more effective antibiotics.

2. Streptothricin. This substance is closely related to streptomycin. Its properties are similar, but it is even more toxic, and has been little used except experimentally.

3. Subtilin and Mycosubtilin, as the names imply, are derived from a strain of *Bacillus subtilis*. Their antibiotic spectrum is similar to that of penicillin and in addition they are effective *in vitro* against the tubercle bacillus. They have

been used experimentally to a limited extent, together with streptomycin, in the chemotherapy of tuberculosis, but success was only moderate.

4. Circulin or Q19 obtained from cultures of *Bacillus circulans,* is highly active against the gram-negative bacilli, but does not have a margin of safety adequate for therapeutic use in humans.

5. Chlorophyll has some degree of bacteriostatic activity, but is low in bactericidal power. It has been found to be therapeutically effective in topical application by virtue of its stimulation of tissue repair and of promotion of wound healing. It also creates an unfavorable environment for bacterial growth. It would be difficult, however, to advocate reliance on this substance in preference to other immeasurably more potent antibiotics.

6. Antifungal Antibiotics. A large group of these substances are being currently investigated in the hope of finding some substance capable of controlling the virulent deep mycoses. Some of the agents display a degree of promise: tomatin, antibiotic XG, fradicin, etc. One of them called prodigiosin and extracted from a filtrate of a culture of *Serratia marcescens* (*B. prodigiosus*) was found to be fungistatic against *Coccidioides immitis* in dilutions of 1:500,000 and fungicidal at 1:100,000[38]. It may well be that one of these drugs, or some other substance, may actually succed in combatting fungal infections. Further developments will be awaited with great anticipation.

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The entire concept of therapy of infectious diseases has changed so completely within the past few years that practically every treatment more than a few years old is already obsolete. If progress continues in the whirlwind pace it has maintained up to now, the outlook for the control of infectious diseases is bright indeed.

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CONDITIONS SIMULATING CONGESTIVE HEART FAILURE*

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Many diseases resemble congestive heart failure. Some, such as myxedema,[1] beriberi,[2] thyrotoxicosis,[3] pernicious anemia,[4] and glomerulonephritis,[5] are well-known. Others, like the rapid non-organic cardiac rhythms or arrythmias,[6] neoplasms,[7] scurvy,[8] cirrhosis of the liver,[9] dissecting aneurysm of the aorta,[10] chest deformities,[11] chronic constrictive pericarditis,[12] arteriovenous aneurysm or fistula,[13] spontaneous mediastinal emphysema,[14] secondary (iron-deficiency) anemias,[15] sickle-cell anemia,[16] scleroderma,[17] and primary cardiac amyloidosis,[18] seldom are considered in the differential diagnosis of cardiac failure. Many of the latter are rare, but they do occur, and require consideration when patients are being treated for so-called "intractable" heart failure.

Report of Cases

Case 1. M.B., a 59 year old white male, complained of dyspnea of one year duration, edema of the lower extremities and a cough for the previous 2 months. For many years he had imbibed heavily of alcoholic beverages. The year before he developed the above symptoms he had undergone 3 urinary bladder operations for acute retention, calculi, and a prostatectomy. He had recently been on a 3 week strict cardiac regime of digitalis, parenteral mercurial diuretics, and a low sodium diet, without any apparent improvement.

Physical examination revealed a poorly nourished dyspneic male whose blood pressure was 118/70. The veins in the neck were distended. There were impaired resonance and crepitant rales at the bases of both lungs. The left heart border was 12 cm. from the midsternal line, and the heart tones were very distant. The liver was not palpable, but a marked pitting edema of the lower extremities was present.

Laboratory examination showed 2+ albumin in the urine, with an occasional hyaline cast. The hemoglobin was 45%, RBC of 2,850,000, and WBC of 10,150. The differential blood picture showed minor abnormalities of the red cells. The urea nitrogen content of the blood was 25.2 mgms. per 100 cc., creatinine of 1.8, cholesterol of 185, and sugar of 111. Kahn reaction of the blood was negative. A chest x-ray was interpreted as showing moderate cardiac enlargement. The electrocardiogram showed a rate of 80, left axis deviation, a P-R interval of 0.24 sec., low T waves, and all QRS complexes of low amplitude with slurring in all leads. When all the factors that could cause the clinical picture in this patient were considered, it was decided to use a high vitamin diet and thiamin by injection. He responded slowly to this management, but recovered fully within 2½ months.

All the criteria for the diagnosis of occidental beriberi heart disease described by Blankenhorn[2h] were considered in this patient. These include: (1) insufficient evidence of other etiology since this patient had no evidence of rheumatic, hypertensive, coronary, luetic, thyrotoxic, or bacterial heart disease, (2) three or more months on a thiamin-deficient diet, which was the most prominent feature in the history, as he was not only a chronic alcoholic but had been on restricted diet both for the bladder and cardiac disturbances, (3) signs of neuritis or pellagra; although neither of these was evident, it was the only criterion absent (not all cases developed such manifestations); (4) dependent edema, which was present as a constant feature and was not altered by previous treatment, (5) elevated venous pressure; although this was not determined by direct measurement, it was evident in the distended cervical veins, (6) minor electrocardiographic changes, which were present, but could not be determined definitely as due to the previous digitalis or to the beriberi; the changes disappeared as the patient improved, (7) recovery with a decrease in heart size, which was a prominent feature in this patient. The importance of superimposed etiological factors, such as anemia, infection, and exertion, has been stressed.[2j] This patient had had a blad-

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der infection, and anemia was present. If the three operations may be considered as exertion, all the extra etiological factors were present.

Case 2. M.R., a 58 year old white female, had original complaints of dyspnea and edema of the lower extremities. For 18 months she had been treated by absolute bed-rest, a variety of digitalis preparations, and a host of diuretics, with little improvement.

Physical examination revealed an emaciated female with blood pressure of 146/20; her skin was moist and warm. The thyroid gland was palpable, firm and nodular. There were no findings of pulmonary congestion. The left heart border was 14 cm. from the midsternal line, and the heart sounds were hyperactive. Auricular fibrillation was present. The liver was not palpable, but there was moderate edema of the lower extremities.

Laboratory examination revealed no abnormalities in the urine or of the hematological picture. The Kahn test was negative. Urea nitrogen was 20.5 and blood sugar was 106. An x-ray of the chest was interpreted as showing marked cardiac enlargement. In the electrocardiogram the rate was 110, with signs indicative of auricular fibrillation. Repeated basal metabolic rates on three consecutive days showed an average of +73%. She was placed on a management including iodine and a high caloric diet, but suddenly expired 9 days after such treatment was instituted. An autopsy was not obtained.

This patient was said to be in "intractable" failure, and all the possible etiological factors were considered. Thyrotoxicosis not infrequently is the sole cause of congestive heart failure.[3b] It is more likely to occur in the female sex, with increasing age, when the thyrotoxic state lasts longer and when auricular fibrillation is present. Aside from hyperthyroidism, there are many causes of an elevated basal metabolism, all of which cause an increase in oxygen consumption. Factors such as hypertension, polycythemia, leukemia, pregnancy, coarctation of the aorta, and cardiac failure associated with beriberi could be excluded in this patient. The most important cause of an elevated basal metabolism, other than hyperthyroidism, is congestive heart failure. In the acute stage the basal reading may reach +75%, but seldom does it reach such a height in a chronic case. The other features, the moist warm skin, loss of considerable weight despite a good appetite, hyperactive heart sounds, failure of the fibrillating heart to slow on adequate digitalis, and the high pulse pressure, suggested the hyperthyroidism. Aortic stenosis with elevated metabolic rates simulating hyperthyroidism has been reported as another cause to be differentiated, but the highest metabolic rate in such cases was +53%.[3e]

Case 3. M.U., a 57 year old white male, complained of dyspnea, palpitation, and edema of the ankles, all of 3 months' duration. His past history was negative. He had been on a regime of absolute bed-rest, digitalis, low-sodium diet, and diuretics for 2½ of the 3 months, without improvement.

On physical examination he appeared very pale, but lay in a recumbent position without apparent dyspnea. His blood pressure was 120/54, and the tongue was smooth and glossy. The left heart border was 15 cm. and the right 4 cm. from the midsternal line. A loud systolic murmur was audible over the entire precordium. The liver and spleen were not palpable. Edema of the lower extremities was moderate.

Laboratory examination of the urine was negative. The blood study showed 18% hemoglobin, 610,000 red blood cells, a color index of 1.5, and 4,300 white blood cells. There was a normal differential count, but the red cells showed all the signs of a severe anemia. Reticulocytes were 3.8%. The Ewald test meal showed 0° free acid and a total acid of 6°. Blood Kahn was negative. The urea nitrogen was 30.8, creatinine 2, sugar 112, and the icterus index 8. A chest x-ray was interpreted as showing marked cardiac enlargement. The electrocardiogram revealed a rate of 96, left axis deviation, T_1 isoelectric, T_2 and T_3 diphasic. Under treatment with liver by injection daily he responded well and rapidly.

Carter and Traut,[4] who noted cardiovascular manifestations in 257 of 300 cases of pernicious anemia, felt that in the presence of a severe anemia it may be impossible to segregate dependably patients with primary cardiac involvement. Examination of the blood is essential for dependable differentiation. Anemia (primary or secondary, and not uncommonly the latter) gives rise to a loud systolic murmur heard best at the apex.[19]

Case 4. J.S., a 43 year old white male, com-

plained of dyspnea and edema of the ankles of one month duration. He had been on a strict cardiac management, including digitalis, but there was no improvement. The past history was noncontributory; only that he had pneumonia 3 years earlier.

On physical examination he appeared pale, dyspneic, restless, and apprehensive. The blood pressure was 180/100. There was no icterus. Crepitant rales were audible over both lung fields. The left heart border was 9 cm. from the midsternal line, and a reduplicated first heart sound was audible at the apex. The liver was not palpable. There was marked pitting edema of the lower extremities.

Urinanalysis showed 4+ albumin, 4+ blood, many red blood cells, and many hyaline, red blood cell and granular casts in the microscopic picture. The specific gravity was fixed between 1.012 and 1.015. Blood Kahn reaction was negative. The blood picture showed a hemoglobin of 55%, a red cell count of 2,975,000, and a white count of 22,000 with a differential of 88% polys and 12% lymphs. The urea nitrogen was 37 and the creatinine 2.3. Electrocardiograms showed a rate of 100, no axis deviation, and the T in Leads 1 and 2 negative. An x-ray of the chest showed no abnormalities. The total protein was 5.2, with albumin 3.1 and globulin 2.1, and an A/G ratio of 1.5:1. The patient continued on absolute bed rest until the red blood cells disappeared from the urine, which occurred within 7 weeks.

Cardiac complications are fairly frequent in acute glomerulonephritis, and patients who die during the acute phase may expire from heart failure. Odel and Tinney[5e] found evidence of obvious cardiac involvement in 16% of 136 cases of acute glomerulonephritis. These cardiac complications varied from murmurs, with or without dilatation, to manifestations of severe cardiac decompensation. Although digitalis is indicated and used in congestive heart failure complicating acute glomerulonephritis, it is of little value during the acute stage. In instances where the congestive failure is a complicating factor, the patient may die suddenly or may improve rapidly, leaving no demonstrable evidence of organic heart disease. The importance of hypertension in the pathogenesis and relief of the congestive failure which frequently complicates acute glomerulonephritis has been emphasized.[5d] However, while this may play an important role in many cases, it may not be the only factor.[5f]

Case 5. C.E., a 53 year old white male, complained of dyspnea, weakness, and swelling of the lower extremities of 5 months' duration. The past history was negative, except that he had been treated intensively with digitalis and diuretics for over 4 months, and he had been on absolute bed-rest for the previous 6 weeks without improvement.

On physical examination he appeared chronically ill and emaciated. The chest was emphysematous, and numerous crepitant and coarse rales were audible over both lungs. His blood pressure was 110/90. There was no icterus. Cardiac findings were not abnormal. The liver was palpable 2 fingers breadth below the right costal margin, but was not tender. The lower extremities showed a marked waxy pitting edema.

The urine was negative on laboratory examination. Hemoglobin was 80%, red cell count 3,740,000 and the white cells 5,100; the differential blood smear appeared not unusual. Blood Kahn reaction was negative. Electrocardiograms revealed a rate of 88, extremely low amplitude of the QRS complexes, and isoelectric T waves in all leads. A chest x-ray was unrevealing. Fluoroscopy and x-ray examination of the stomach and duodenum was interpreted as showing an extensive deformity of the pylorus and the pars media of the stomach, most likely due to carcinoma.

The patient expired 16 days later, and an autopsy revealed (1) a disc-shaped adenocarcinoma of the posterior wall of the stomach, with (2) local metastases to the wall of the stomach, (3) metastases to the perigastric, peripancreatic and peribiliary lymph nodes, (4) focal and confluent bronchopneumonia in both lower pulmonary lobes, (5) brown atrophy and parenchymatous degeneration of the myocardium, and (6) generalized anasarca and emaciation.

The symptoms and findings in this patient did not suggest any involvement of the stomach. His appetite had been good, and he had neither anorexia, nausea, vomiting, epigastric distress, belching, or eructations. His appearance, 5 months after the onset of dyspnea, suggested a malignancy. Such conditions occur, regardless of the age of the patient.[7b,c]

Case 6. U.B., a 45 year old colored female, complained of dyspnea, palpitation, and tachycardia of 6 months' duration. She was a gravida

VI, para III, with a history of 3 miscarriages in the first three pregnancies.

On physical examination the conjunctival and oral mucosae appeared pale. The blood pressure was 140/78. There was no icterus. The left heart border was 12 cm. from the midsternal line and there was a loud systolic murmur at the apex. Liver was 4 fingers breadth below the right costal margin. Marked edema was evident in both lower extremities. Abdominal palpation revealed a hard mass in the lower portion above the pubis. On vaginal examination a large, hard uterus, the size of a grapefruit, was palpated, and there was gross blood on the examining fingers.

Catheterized specimens of urine were negative. The hemoglobin was 42%, RBC of 2,800,000, with a WBC of 12,000 and a normal differential picture. Blood Kahn test was negative. Electrocardiograms showed a rate of 130, left axis deviation, T_3 negative, and notching of the main complexes. X-ray examination of the chest, gallbladder, stomach, duodenum, and colon showed no abnormalities.

This entire clinical picture was reversed by giving the patient multiple blood transfusions, followed by hysterectomy. Anemia, causing a condition that simulated congestive heart failure, has been reported. Bartels[15a] illustrated this in a case of secondary anemia due to a bleeding duodenal ulcer. Schwartz and Blumenthal[15b] studied 20 patients who had diaphragmatic hiatus hernias with severe iron-deficiency anemia, and found cardiovascular symptoms in 12 (60%). With the exception of active rheumatic infection, bacterial endocarditis, periarteritis nodosa, disseminated lupus erythematosus and advanced tricuspid disease, organic cardiovascular disease does not cause anemia.[20]

Case 7. J.F., a 68 year old white male, complained of dyspnea, orthopnea, and swelling of the legs of 10 days' duration. The past history, except for digitalis therapy, was not elicited at the time because of the gravity of the situation.

On physical examination the blood pressure was 130/70 in an acutely ill patient who appeared to be in great distress. There were crepitant rales audible over both lung fields. The left heart border was 18 cm. and the right border 5 cm. from the midsternal line. Heart tones were very distant. The ankles and legs were swollen, but it was a brawny induration. Examination of the mouth revealed edentulous gums that were markedly swollen, tender, and bled easily on touch.

Laboratory examination showed a negative urine, a hemoglobin of 72%, RBC of 3,200,000, WBC of 9,240 with a normal differential picture. The urea nitrogen was 23.4. A chest x-ray was interpreted as showing marked cardiac enlargement. An electrocardiogram showed a rate of 80 and isoelectric T waves. Vitamin C determinations on the urine and blood showed both to be devoid of reduced ascorbic acid. The use of adequate diet with additional Vitamin C brought about the full recovery of the patient within 3 weeks.

The criteria of the diagnosis of scurvy are: (1) a history of dietary inadequacy of Vitamin C or the presence of some condition that is known to increase the requirements of Vitamin C, (2) the physical findings characteristic of the scorbutic state, and (3) Vitamin C determinations on the blood and urine.[8b] Classic signs of adult scurvy are large cutaneous hemorrhages, hemorrhagic follicular keratosis and hemorrhagic gingivitis, and anemia.[8c] In a ten year study at the Cincinnati General Hospital, scurvy was diagnosed 33 times.[8d] It occurs almost entirely in men over 60 who live alone or in lodgings. They do not have to be especially addicted to alcohol, but they do not eat fruit or uncooked vegetables. Experimentally,[8a] it has been demonstrated that scurvy carditis does occur and resembles lesions due to acute rheumatic fever. However, Weiss and Wilkins[2c] felt that cardiac disturbances in human scurvy, with the exception of hemorrhagic pericarditis, are usually due to co-exisiting Vitamin B_1 deficiency.

Case 8. F.Z., a 45 year old white male, complained of dyspnea and precordial pain of 4 months' duration. He was a known hypertensive of 20 years' standing. During the last 2 months of the present complaints he had been on a strict cardiac regime.

On physical examination the blood pressure was 186/70. There was no icterus. Numerous crepitant rales were audible over both lung fields. The left heart border was 11 cm. from the midsternal line, and a loud systolic murmur was audible over the apex. The liver was 3 fingers breadth below the right costal margin, not tender, and the spleen was firm, palpable 7 fingers

breadth below the left costal margin. Edema was absent.

Laboratory examination of the urine showed 4+ albumin, 4+ blood, and numerous red blood cells. The hemoglobin was 40%, RBC of 2,200,000, WBC of 11,240, with a normal differential picture. Blood Kahn was negative. Electrocardiograms showed a sinus rate of 110 with a left axis deviation. During the next 10 days the urea nitrogen rose to 87.6 and the creatinine to 8. He expired in uremia with a clinical diagnosis of congestive heart failure due to hypertensive heart disease.

Autopsy revealed (1) atrophic cirrhosis of the liver with dilatation of the bile ducts, (2) marked splenomegaly, (3) bronchopneumonia involving all the lobes, (4) marked dilatation of the esophageal, inferior mesenteric, splenic, and paraumbilical veins, and (5) pseudomembranous cystitis.

This patient had complaints and findings common to both congestive heart failure and to cirrhosis of the liver. Dyspnea is the most frequent symptom in congestive failure, but occurs in 20% of cirrhotic patients.[9] The presence of anemia is not common in hypertensives except when uremia occurs, but is frequent in cirrhosis. Considerable discussion evolved about the splenomegaly in this patient. It has long been a general impression that the spleen does not become palpably enlarged as a result of congestive heart failure.[21] As a corollary of this, it has been felt that if the spleen is palpable in a case of heart failure, some complication should be suspected.[22] Splenomegaly has been reported singly,[23] and varying from 3% to 23% in series of cases of uncomplicated congestive heart failure.[24, 25, 26, 27] Therefore, a palpable spleen alone cannot be said to be specifically for or against the diagnosis of congestive heart failure.

Case 9. B.H., a 50 year old white male, had dyspnea, ascites, and edema of the lower extremities for 2 years. Intensive cardiac treatment had been carried on in 5 periods of prolonged hospitalization during this period.

On physical examination marked cyanosis was present. The blood pressure was 200/130. Edema of the face was noted. The left heart border was 15 cm. from the midsternal line, and there was an intense, loud systolic murmur audible over the entire precordium. Generalized anasarca was present.

Laboratory examination revealed 4+ albumin and many hyaline casts in the urine, a normal blood picture, a negative Kahn, urea nitrogen of 13.7, a chest x-ray interpreted as showing marked cardiac enlargement, and electrocardiogram with a rate of 84, left axis deviation, negative T waves in all leads, and marked slurring and notching in all the main complexes. Prolonged treatment for 5 months failed to bring any improvement and when he expired, the final clinical diagnosis was malignant nephrosclerosis.

Autopsy revealed (1) a dissecting aneurysm of the descending aorta with marked atheromatosis of the double-barrelled aorta, (2) thrombosis of the lower end of the newly formed lumen of the aorta, (3) marked eccentric hypertrophy of the heart, (4) chronic passive congestion of the liver, lungs, kidneys, and spleen, (5) right hydrothorax, hemopericardium, and ascites, and, (6) generalized anasarca.

Among 19 cases of dissecting aneurysm previously described, 12 had a gradual onset of symptoms and signs.[10a] The outstanding feature of these old, "silent" dissections was the "intractable" heart failure. In 44 cases analyzed by Baer and Goldburgh,[10b] 15 presented signs of cardiac failure. When "intractable" failure does occur in such patients, there is little basis for venturing a diagnosis of dissecting aneurysm. Single cases are mentioned by others.[10c, d] With the report by Golden and Weems,[28] where a definitive diagnosis of dissecting aneurysm was made by angiocardiography (and later confirmed at operation), an entirely new approach into this extremely difficult subject has been opened.

Case 10. S.R., a white male, was 32 years old when first seen in July, 1934. At that time he stated he had been taking 12 grains of quinidine daily since February, 1929, except for one short period in 1931. In that period he had stopped taking the quinidine, following which he developed auricular fibrillation and congestive failure, necessitating hospitalization. When first seen in 1934 he had no complaints, only wanting to know whether he should continue the drug.

Physical examination revealed a comfortable patient, whose blood pressure was 126/70. The apical impulse was not visible or palpable. The left heart border was 10 cm. from the midsternal line in the fifth interspace. The heart tones were

soft and distant over the entire precordium in all positions, upright, recumbent, and on the left side, before and after exercise. The rate was 54 and the rhythm was regular. The liver was not palpable.

All laboratory tests were within normal limits. An electrocardiogram, taken on July 12, 1934 showed a rate of 70, low amplitude, and slurring of all the main complexes.

The quinidine was stopped on July 17, 1934 and an electrocardiogram taken on August 23, 1934 showed a rate of 70 and a negative T_3. On September 20, 1934, after being without quinidine for 7 weeks, he developed a rapid auricular fibrillation, confirmed by an electrocardiogram. Within a week after the arrythmia appeared, he began to have symptoms and signs of congestive heart failure. Treatment with quinidine was started and after taking 46 grains, an electrocardiogram showed a rate of 80, left axis deviation, all T waves negative, and the main complexes slurred. The symptoms and signs of failure disappeared. During the rest of 1934 and during 1935 he continued to take 12 grains of quinidine daily and had no recurrence. In 1936 he stopped the drug on 2 occasions. In July, 1936 he fibrillated for one month and became decompensated; 176 grains of quinidine restored regular rhythm and the congestive failure disappeared. The recurrence in October, 1936 was less severe and cleared on 36 grains. From December, 1936 to December, 1949, when last seen, he took quinidine daily and did not have any recurrences.

This patient has been on quinidine 20 years. He developed failure approximately 6 weeks after the drug was discontinued. The rapid arrythmia continued on the average 20 days before failure appeared. Each time the drug converted it to regular rhythm and compensation was restored after an average of 46 grains had been ingested over an average of 5 days.

Emphasis has been placed on the frequency of auricular fibrillation occurring without evidence of organic heart disease,[6a, 6b] the good prognosis,[6b, 6e] and its relation to congestive heart failure.[6c, 6d] One patient in Hanson and Rutledge's[6i] group of 30 cases has been on a maintenance dose of quinidine for 15 years and attacks still occur when the drug is stopped. Congestive failure may occur due to auricular flutter,[6a, 6b] paroxysmal ventricular tachycardia,[6f, 6h] and to supraventricular tachycardia,[1d] all in the absence of demonstrable heart disease.

Discussion

Among these ten cases, certain factors appear prominent. Electrocardiographic changes were present in nine, anemia of some degree in seven, and thiamin deficiency, either on a theoretical or a practical basis, in six.

Too much emphasis can be placed on the position of electrocardiography in the diagnosis of heart disease. Minor changes in the tracings are frequently termed as being "compatible with myocardial damage." The major reason for this abuse is that the limitations of the electrocardiogram have not been properly recognized. Sensenbach[29] listed eleven drugs, nine acute infections, and fourteen metabolic disorders, among forty-seven different conditions not due to primary disease of the heart, which may be associated with changes in the electrocardiogram similar to those caused by coronary sclerosis and myocardial damage.

Numerous studies of the electrocardiogram in chronic anemia indicate, that, while abnormalities occur in approximately a quarter or more of such patients, they are minor in degree and are not specific for anemia.[20] Prolongation of the Q-T interval,[30] flattening or inversion of the T in one or more leads,[31] low amplitude,[32] transitory prolongation of the P-R interval,[33] and depression of the S-T segment[34] have been noted. The possibility of Vitamin B_1 deficiency, digitalis administration, especially digitoxin,[35] and in some patients, the effect of the disease responsible for the anemia, are difficult to exclude as causes of electrocardiographic changes.

Summary.

Many conditions simulate congestive heart failure. Some of these (myxedema, beriberi, thyrotoxicosis, pernicious anemia, acute glomerulonephritis, rapid nonorganic cardiac rhythms or arrythmias, scurvy, secondary anemia, and arteriovenous aneurysms) are completely reversible under selective therapy. The use of a rigid cardiac management including digitalis, diuretics, and a low-sodium diet, is not effective in the variety of conditions mentioned. Failure of these thera-

peutic agents in the treatment of such cases does not mean that the patient is in "intractable" failure. Individual management is mandatory for the treatment of these conditions which simulate congestive heart failure.

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(Continued on page 65)

THE BIOLOGICAL PROOF OF PATERNITY*

LEONE LATTES, M.D.**

For many years I have advocated the rational application of biological knowledge to the judicial problems of paternity, and I have made persistent efforts to obtain recognition and acceptance by the jurisprudence of the brilliant results of biological investigation.

The problem is indeed very old. The opposition of jurists to the acceptance of biological proofs remained justified for a long time. Indeed, the conflict of opposing interests forced jurists to pay attention to the problem long before its scientific solution was even a remote possibility. As sufficient biological knowledge was lacking, those who had to express an opinion either declared the problem to be insoluble, or, anxious to reach a decision at any cost, came to the oddest conclusions. This is why the juridical investigation of paternity passed through so many vissicitudes; for the legislators were urged on by grave reasons of equity and morals clamoring for a theoretical solution of the problem, while they were at the same time confronted with the lack of scientific proofs.

Against the persistent sense of moral and social injustice felt by the illegitimate mother and her offspring, there is always raised the granitic obstacle of the Napoleonic postulate that nature covers human reproduction with an impenetrable veil and that it is, therefore, impossible to obtain direct and certain proof of paternity. For this reason, if on the one hand the fair sex is handicapped by the prohibition to investigate paternity, on the other hand, there exists a simple but implacable rule which says: the husband is the father of all children conceived during the marriage. As Balzac puts it, "The flag protects the merchandise."

Only the resounding success obtained by the study of blood groups could overcome this obstinate resistance, a fact which was not recognized by a high judicial body until 1932 when the Italian Supreme Court admitted the value of blood groups in a now famous decision.

It must, however, be recognized that Italian legislation, like that of other Latin countries in Europe, was definitely opposed to a wider application of biological proof, and such proof could be brought to bear upon in no more than a very limited number of exceptional cases. The matter was entirely different in the Latin-American countries, where the geographical and social structure obviously is very favorable to its application.

It is true that ten years ago, when I arrived in South America, there was scarcely any practical application of this kind of proof, but the juridical and social ground was well prepared. I cannot forget the impression I received when upon landing, I was immediately invited to collaborate in the solution of a number of important cases that were brought to trial. Since then, the courts have adopted a broad view concerning the value of biological proof, which is unequaled in countries with an older juridical tradition. And this is especially true with respect to the problem of natural offsprings.

It happens quite frequently that bachelors are sued, on behalf of natural offsprings, by women with whom they had intercourse, or that suits are brought to claim rights of inheritance. In these circumstances the action can be successfully brought only on a solid basis of testimonial and documentary evidence. However useful and important such evidence may be, it often meets with the obstacle of the proof of the woman's promiscuity at the time of conception, which the Roman law calls the *"exceptio plurium concumbentium."* Juridical arguments can never eliminate the *"exceptio plurium concumbentium,"* as only a biological proof can clear the situation. There is an old proverb full of malice:

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the children of my daughter are my grandchildren; only God knows the children of my sons.

Formerly, confronted with the *exceptio plurium*, the judge was faced with the natural mystery of human generation, and had to declare that paternity had been proven. Therefore, only the husband was excluded from the benefits of the *exceptio plurium*, as he was legally presumed to be the father.

There exists, however, an argument to clarify the relationship, which was already used in antiquity, namely that of the likeness between the child and the supposed father, a likeness which sometimes is easily observable and based on a coincidence of objective somatic traits. However, the probative value of the transmission of individual traits which belong to the ordinary, normal elements of likeness, be they anatomical, biochemical or functional, could only be based on solid grounds when the science of genetics came into being.

There can be no doubt that the Mendelian rules constitute the most solid part, if not the whole, of what is at present known about heredity. Most scientists consider them as laws of general biological validity applicable also to man.

For readers who know the subject, I need not dwell upon the importance of the concepts of dominance and recessiveness in heredity. It is current knowledge that a dominant trait can be pure or hybrid (heterozygous) containing the recessive trait in a latent state; whereas the recessive trait is always pure and cannot carry the dominant trait in a latent state. It is therefore clear that, given a pair of hereditary traits about whose dominance and recessiveness no doubt is left, the medico-legal and juridical application is immediately possible.

The answer that biology can give to the problem in question is the following: either that the offspring is compatible or that it is incompatible with a given pair of parents. And such a relation, evidently, links the offspring in exactly the same way to the man as to the woman in this pair. However, in nearly all cases the juridical answer takes a different aspect, because the relationship between the mother and the child is either proved or admitted. Therefore, the problem is usually not that of blood relationship in general, but that of the paternity of a man, with respect to a given pair or "constellation" of mother and child. And the possible answers are therefore: compatible father or incompatible father.

These two answers have a very different value. The second, incompatible father is final and decisive. On the other hand, although the first answer is in itself also clear from the biological standpoint, it contributes only in a vague and indirect way to the solution of the judicial problem. For, "compatibility" means that the person who has been examined could be the real father, but also leaves the possibility that he might not be.

Such compatibility can exist in two degrees: the offspring can be a recessive and show dominant characteristics existing in the mother, in which case the father, generally speaking, can be anybody. In other cases, however, the offspring is dominant and the mother recessive and, therefore, the type of the real father must necessarily be dominant. If the presumed father does not fulfill this condition, we get the case of incompatibility, or, in other words, he is excluded. If he does fulfill this condition, there is a compatibility in which a discriminating prediction is fulfilled. In spite of the fact that it cannot lead to any judicial decision, it has in practice often had a psychological effect in convincing the seducer that the child of the seduced woman was really his. Now the educated public, knowing about the practical possibility of excluding the wrong father even by means of a single incompatible trait, objects that this does not constitute positive proof of paternity. And this they say half disillusioned and half appeased, as if realizing the revolutionary implications of the complete solution.

There can be no doubt that the final aim of science is the direct and complete proof of paternity with respect to a given "constellation" of mother and child. And in this long way we are not as far from the solution of this problem

as the proponents of the old principle *"father semper incertus"*—the father is always doubtful—may think; but, on the other hand, we are not yet so far ahead as many wishful thinkers would like. We may already say that this proof is no longer an utopian idea; but the final and indisputable triumph will yet require much patience and much work.

Certainly in some exceptional cases, very rare anatomical or functional anomalies on the borderline of hereditary illnesses such as the white lock of hair, polydactylism, brachydactylism, hemophilia, color blindness, etc., when they occur simultaneously in the offspring and the presumed father are probative evidence, which is of great help in some cases. I would like to tell you the story of two of my best cases.

The first case, which is of great interest because of its penal nature, demonstrates how the judicial question may be resolved, supplementing hereditary data with medical elements of a different nature. This case is also peculiar in that it represents an attempt to change the state of a legitimate child to that of a natural one. The story centers around a girl who had two birth certificates. The first time she was recorded as the natural child of an unmarried woman. A certificate recorded two years later declared her the legitimate child of a married couple. The two mothers were sisters. When the child was 11 (or 13), the unmarried woman brought suit against her sister and brother-in-law, accusing them of falsely declaring the birth of the child before the court. This was done to recover custody of the daughter and, incidentally, allow her to claim inheritance of the estate of the deceased natural father. The medico-legal problem in this case was double: the determination of paternity and that of maternity. A first investigation of the married couple revealed the following: husband group AN, wife group OM, disputed daughter BM. The husband could, therefore, be excluded as father of the child on two counts: because he was A and because he was N. The wife could not be ruled out as mother; however, the probability of her being the real mother was much smaller than that of her sister, the plaintiff, who belonged to the same blood group and type (BM) of the disputed child. This difference in probabilities, however, could not be decisive. At this point we suggested a gynecological examination of the two women. The plaintiff, who meanwhile married another man and had several children, showed genitals of a multipara with typical *caruncolae mirtiformes*. The defender instead, showed a virginal cervical os and a vulva with complete preservation of the hymen, although lacerated. The woman was undoubtedly a nullipara. We were, therefore, able to exclude also the maternity and the legitimate child was legally declared the natural daughter of the plaintiff. The defendants were condemned to two years in jail and to a fine of $50,000.

The second case is the story of a suit which had been pending for 12 years and involving several million dollars which was dramatically ended by a direct demonstration of paternity by means of evidence never before obtained. Mr. E. P. was an eccentric and rich land-owner who lived in a country house with a common-law wife named A. C. A. C. went back to her home and, after an adequate number of months gave birth to a child, who will be the heroine of our story. Mr. E. P. considered the child his own and supported her. In 1937 Mr. P. died of cancer after long illness during which he received numerous blood transfusions and had his blood group recorded as A. The following year the mother began action for the legal recognition of the paternity of the dead man, but the heirs designated in Mr. P.'s will brought suit against this action, claiming that during the period in which the child was conceived, the mother had had sexual relations with a servant, and that the daughter could have been the child of this man. A preliminary examination of the blood groups proved the following constellation: mother: group A; daughter: group A; presumed father (dead): group A; suspected father (the servant): group O. Obviously both males or any other male could have been the father of the child. At this point, I

was requested to determine the properties M and N of the three persons alive. In the presence of many witnesses, as this had never before been done in South America, I found the following: mother A M N; daughter A M; servant O N. This allowed me to state with unequivocal certainty that the servant could not have been the father of the child. The servant having failed to help their purposes, the hopeful heirs hired another supposed expert who reasoned that, if the MN examination had eliminated the servant from the picture, it might also eliminate the deceased and rich presumed father. He therefore asked for the exhumation of his body, stating that the characteristics MN could be studied in body residues other than blood, a fact which had been repeatedly and conclusively disproven. The exhumation was ordered by the court, although useless *a priori*, and it took place very solemnly. Perhaps because the expert realized the futility of such an attempt, an investigation of the MN system was not made, and the study was limited to the investigation of the ABO system which also failed due to the condition of the body. This effort was indeed futile in view of the fact that the deceased was known to belong to group A and especially in view of the fact that both mother and daughter were A, any man could have been the father. The attempt to prove the incompatibility of the deceased man as father of the child had failed. At this point I could state with certainty that the servant *was not* the father, but I could not state with equal certainty that the deceased man *was* the father, positive proof of paternity being not yet available. What makes this case unusual is the fact that positive proof could be obtained by other medico-legal means. The girl had a frontal lock of white hair and a pigmented mole on her eye-brow. These are two features the hereditary character of which is generally admitted. Did the deceased man also have a lock of white hair and a pigmented mole? The statements of witnesses were contradictory. There followed an endless discussion about family pictures, statements of witnesses pro and con, precocious graying and artificial dyeing of the hair. The evidence was finally accepted, and the real father recognized by a well integrated set of negative and positive biological elements, and by juridical evidence which altogether gave incontrovertible and final proof. This was a fortunate case because abnormal hereditary traits were present. When only one or two normal characteristics are available, the probability of proving the paternity of a compatible man is so small as to disappear for all practical purposes. However, it is evident that this probability increases considerably with the number of the hereditary traits. It is not possible to give an abstract rule for this increase, for the dominant and recessive traits are not uniformly distributed in the population. Moreover, even the most reliable hereditary traits do not all follow the Mendelian rule of heredity. In general, it may be said, that when the number of traits under consideration increases in arithmetical progression, the probability of arriving at a positive decision increases in geometrical progression.

Of course, however great the number of traits may be, mathematical certainty would never be reached; for a mere probability, even if expressed by a very great number, would not be decisive in theory, and the opposite possibility could never be completely excluded.

But the mathematical evidence is one thing, and the biological and forensic reality is quite another thing. For instance, experts and judges all accept as indisputable proof of identity of the individual the absence of discrepancies and the coincidence of a number of characteristic points in a set of fingerprints, in spite of Galton's calculation that two identical fingerprints may occur once in 64 billion.

The same reasoning applies to paternity. The demonstration of the compatibility of the offspring and the presumed father with respect to a great number of traits, the laws of heredity for which must be beyond doubt, and with respect to which there should be no incompatible divergencies, is practically equivalent to the positive proof of paternity. It re-

mains to be established what should be understood by the words "a great number." Mathematically the expression has no meaning; but not so in the natural and social sciences, where it must be interpreted in accordance with the problem under investigation.

In the case we are considering, it may be stated that the positive and direct proof of paternity could be achieved in all cases the day we have at our disposal a couple of dozen of hereditary traits whose transmission should be ruled by a clearly defined Mendelian law of recessiveness and dominance, and whose objective manifestations, be they anatomical, functional or biochemical are not open to doubt. Biological investigation has not yet won this triumph, although constant efforts bring it ever nearer to this goal.

The investigation of paternity has become scientific since the so called "blood test", founded on the dominance of the Landsteiner's antigens A and B, has come into existence. Several juridical decisions are based exclusively on these properties, to the total exclusion of the formerly utilized physiognomic traits. Now the probability of success on the basis of the inheritance of blood groups varies considerably, according to calculations, with the group to which the presumed father belongs; in total the probability of exclusion is about one-sixth of all cases.

It may seem trivial, but the possibility of a definite elimination had a profound effect on the psychology of the public, which became aware that the mystery of generation was no longer impenetrable and that, therefore, certain false and interested accusations might prove dangerous. There was, moreover, a very stimulating effect on the investigators, who felt the urge to look for other hereditary qualities of the same probative efficacy. Before all, the biochemical substances contained in the blood and other tissues were studied more profoundly, and promising and stimulating results were obtained. In the first place, the heredity of the factors M and N was firmly established. These factors were identified by means of the immunizing of rabbits against chosen human blood cells.

Next, another principle was used; namely, that there exist biochemical properties which are traits of the species in certain animals, and, conversely group traits in man. The genius of Landsteiner and Wiener in treating guinea pigs with blood of the monkey *Macacus rhesus*, led to the identification of the Rh system in man, and to discoveries of unexpected importance in the clinical and genetic fields. These discoveries accumulated with incredible rapidity, principally through the noble scientific competition of the North American and British Schools. Because of its greater complexity, the Rh system, as compared with other specific group systems, showed two peculiar characteristics. The first is that the Rh antigens have outstanding immunizing properties from man to man, in such a way that in the conflict of individualities that may spring either from pregnancy or from transfusions, more or less complicated antibodies are easily formed. The human serums in which they accumulate have completely replaced the experimental immunized animal serums in diagnostic investigation.

In the second place, and in a way different from the ABO system, the condition of homo and hetero-zygote in the Rhesus system can be put in evidence directly through serological means, at least in a great number of cases. The enormous importance of this circumstance for calculations concerning heredity and also for concrete cases of excluding paternity, should be emphasized. For the Rh system, the genetical doctrine of Fisher, and with it also the British terminology imposed itself, in spite of some not yet quite eliminated doubts. I consider the statement of Race that the theory of Fisher has brought clarity to the observations concerning the system to be quite correct. As is well known, it presupposes a multiple allelomorphism with 3 loci, where in each chromosome three closely linked genes are situated. We are confronted with 6 principal antigenes and two variations, all hereditary in accordance with the usual law that

the antigene cannot appear in the offspring if it does not exist in either one of the parents. If we had the antibodies corresponding to the antigenes at our disposal, it would be theoretically possible to establish 45 distinct geno-types (according to Race); but, as the number of antiserums that are generally available for practical use is smaller, it is obvious that the number of combinations that can be used practically is also smaller.

In spite of this, the study of the Rh system leads to a considerable extension of the possibilities of arriving at exclusion by means of blood tests, and the corresponding results have already been accepted by the courts in this country. They promise to give still wider extension to the old antigenes P and to other new antigenes (like the "Lutheran" and that of Kell, studied by Race, the Si of Wiener and Sonn, the L of Andersen) which as far as I know have not yet been systematized genetically.

Besides the blood properties, which have been the object of latest investigations, other functional properties have also been looked for. A well known property is the presence in the saliva of the substances of group A, B, and O. This property is not accidental, but constitutional and hereditary; their presence is dominant and their absence recessive. It has already been sufficiently studied to permit practical application. Its limitation lies in that, although the investigation is very easy for groups A and B, it is problematic for the group O.

This property of hereditary "functional insufficiency" shows a certain analogy to an abnormality that has been known for a long time, namely color-blindness, often limited to certain colors only. But this abnormality, which is hereditary, has little value in cases of disputed paternity because of its rareness. It stimulated the study of another similar property which is much more frequent and easily verifiable, namely the so called taste-blindness. It was discovered by Fox in 1932 by means of the use of certain synthetic sulphurated substances, the most used of which is phenylthiocarbamide. It was observed that about a third of the population do not perceive the taste of these substances, whereas the others find them extremely bitter. Such taste-blindness is clearly recessive, whereas the sensitivity to the bitter taste is dominant and can be utilized in court. This investigation has certain limitations as compared with the blood properties; it is not applicable to infants, who cannot communicate their sensations of taste, although many children in tender age express their repugnance very clearly when they perceive the bitter taste.

Considering now again the somatic characteristics, there can be no doubt that the elements of the physical appearance as well as other morphological factors, such as fingerprints, shape of the ear, etc., are very individual in their combinations. And the empirical idea that such individual characteristics are often at least partially transmitted to offspring has been held for centuries. It is therefore justified to look here for elements probative of blood relationship. It should be stated, however, that too great enthusiasm in trying to use these factors in concrete cases for scientific advice, leads to exaggerated and perhaps dangerous results.

The so called pre-Mendelian laws of Darwin and Galton have no scientific value whatsoever when applied to an isolated case. Although they may have a certain statistical value, they generally contribute nothing, or only very little, to the solution of forensic problems. There exist, it is true, certain special cases for which the anatomical characteristics are decisive, for example those of the negro features. A review of the examinations practiced in other cases of exceptional characteristics shows, however, that the attempt to utilize resemblance in certain anatomical particularities, such as the disposition of the veins of the retina or of the back of the hands, the folds of the palate, and still more the details of the ear and of the fingerprints was without convincing scientific basis in the knowledge of hereditary transmission. Heredity can also manifest itself in differences, while resemblance can also be the product of mere coincidences. Resemblance,

in order to have appreciable weight in a judgment concerning blood relationship, should be much greater than can generally exist between non-related individuals. At present it may be said that we as yet lack trustworthy investigations concerning the transmission of the aggregate of traits which constitute what may be called the global resemblance.

Even though the influence of heredity may appear generically, it will not be possible to arrive at a solution of the problem no matter how careful the investigation, if the nature and number of Mendelian facts, their dominance or recessiveness, their polymerism and their sex-linkage are not known.

However, this does not mean that all the ordinary physiognomic factors must be rejected as insufficient. This would be exaggerated, because there are among them some for which a simple and constant law of heredity has been established with sufficient certainty. In reality they are not many, but some have a considerable value. The color of the iris, the presence of an aureola, the attachment of the lobe of the ear, the profile of the nose, and to a certain degree, the extreme shades of color of the skin and hair, are of value.

As to the fingerprints, it should be noted that the results in genetics have not been so overwhelmingly successful as those for personal identification. In spite of the numerous investigations that have been carried out and a certain hereditary influence that can be foreseen, the concrete results are decidedly negative. Nobody would nowadays have the courage to exclude paternity, on the basis of the supposed recessiveness of certain papillary patterns.

There exist, altogether, a small number of physiognomic characteristics which can and must be accepted within the framework of a Mendelian appreciation sufficiently simple to permit a practical application at least in a certain number of cases.

We have, therefore, at our disposal, a score of normal hereditary physiognomic properties whose utilization can be considered as scientifically justified. It should be understood that the investigations on which they are based have not been equally well controlled in all cases, and therefore, their importance for the proof of exclusion is not the same for all. For example, if the exclusion of a supposed father has been, and is, justified in legal practice because of his deviations from the Mendelian predictions in blood groups or eye-color, we might still hesitate in drawing the same conclusion on the basis of a divergence in the whirl of the hair or in the lobe of the ear, cases for which the evidence is insufficient. In the first case there is practical certainty for exclusion; in the second case only a more or less well founded probability exists.

Let us now return to the inverse problem, that is to say the direct proof of paternity, in accordance with the quantitative criteria I have outlined before. If, for all the hereditary traits of recognized value that have been mentioned above, compatibility of the supposed father with the constellation mother and offspring were to be found, it would then be justified to say that this is the real father. If the answer to this question were in the affirmative, this would in reality amount to a solution of the formidable problem of the positive proof of paternity. But in view of the fact that several of the characteristics mentioned cannot be used in all cases, but only in the extreme cases which are the less frequent, and considering that their number is still too low, it may be said that we have not yet achieved as much as all that. Not even compatibility in all these traits is sufficient for the decisive and irrefutable positive proof, as in the inverse case of exclusion. Should we perhaps reject it, because it is beforehand doomed to failure and therefore useless to the ends of justice? Certainly not! Even with its limitations, it can render important services. In any judicial proceedings in which specialized biological investigation is required, elements of another nature, that is juridical, circumstantial and testimonial will never be missing. It is the task of the judge to evaluate all the proofs of varied origin and nature and to arrive at his own

conviction, and therewith to the sentence.

It is no excessive boldness for biologists who care for their profession to say that the achievement of a proof of fatherhood with considerable probability and on a sound scientific basis is, at present, no idle task, but such as to fully justify the laborious investigations involved. Naturally, if the juridical situation limits the possibility of fatherhood to a limited number of men, the compatibility of only one of them would constitute a final and unobjectionable proof of his fatherhood.

But also for the other cases in which a direct proof is required, it is not illogical to foresee that the results already obtained will be consolidated and confirmed in a not too distant future, till they reach the point of certainty. There is *a priori* no reason whatsoever to prevent this. The conquests of the past, which are already highly valued by the jurisprudence, are a good omen for the future.

On the day on which these hopes, long nurtured by biologists, will be fulfilled, the application of our present laws concerning blood-relationship will not only become wider and more human, but these same laws and our customs may at the same time undergo a profound transformation. One of the main pillars of the institution of matrimony and family, namely the legal presumption of the fatherhood of the husband, might even be shaken, and conversely, the juridical institutions destined to regulate the consequences of free sexual relations might take on new vigor.

The possibility of establishing the responsibilities of the father with respect to the fruits of free love will constitute the irrevocable basis for an intrinsic solidarity not only between the father and the mother but also between these and the offspring. The legislator will be able to make this solidarity compulsory by following till the end the way he has already taken; and thus he effects a reality, even outside the traditional institution of matrimony, of the economic and social protection of mother and child which is his principal aim.

There can be no doubt that this could prove socially revolutionary and it is exactly because of the fear of such a subversion that voices, and even voices of authority, are raised to lament the greater extension of the biological proof of natural filiation. I do not share this point of view. Although there may be victims, innocent or guilty, during transitions, it will always be advisable to base our social relations on truth. The great light of truth will put to flight the mists of betrayal, blackmail and abandonment.

HEART FAILURE —

(Continued from page 57)

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DEVELOPMENTAL PATTERNING OF NEURAL CIRCUITS*

R. W. SPERRY, Ph.D.**

The present audience is familiar with the essential features of the histogenesis and the gross morphogenesis of the nervous system, excellent descriptions of which are available in our current textbooks of embryology. With this background we may turn our attention directly to that specialized phase of neurogenesis that deals with the outgrowth of the developing nerve fibers and the establishment of their terminal connections.

With few exceptions, the elongating processes of the developing neurons, insofar as they survive, eventually acquire intimate associations with other cells. The majority, as you know, form synaptic junctions with fellow neurons. Others form endorgan connections of diverse types in the periphery. The patterns of neuronal hook-ups thus formed in the course of ontogeny need to be highly selective and elaborately designed in order to mediate the functions which the developed nervous system must later carry out. In no other organ system of the body do the relations of the individual cell units to one another count so much. The vital importance of precise patterning is well illustrated in the abnormal and often bizarre functional effects (Sperry, 1945c, 1947b) that follow any surgical or accidental rearrangements of the normal neuronal associations.

The ensuing discussion is concerned primarily with the question of how this orderly patterning of fiber connections is achieved in development. Reducing our problem to its simplest terms, it may be stated as follows: How do the outgrowing fibers of the developing neurons manage to acquire their proper endorgan connections in the periphery and their proper synaptic junctions in the ganglia and nerve centers? The emphasis here is on the word "proper" with special regard for the *selectivity* of neuronal connections. From the standpoint of the function of the developed nervous system, this constitutes one of the most important and interesting phases of neural growth. It certainly is one of the most complicated and refined steps of neurogenesis, and also one about which we yet have a great deal to learn.

One of the main issues which has arisen in this field has been the question of the extent to which the neuronal associations are patterned by function, i.e., by some process akin to learning or conditioning, involving experience, trial and error, etc., and the extent, on the other hand, to which the integrative linkages are organized directly in the growth process itself, prior to and independently of function. The problem of the degree to which our brain functions, i.e., our intelligence, our skills, talents, temperaments, etc. are inherently predetermined, is an old one and has widespread practical import.

In the past it has been predominantly assumed that the functional factors are primary. The integrative circuits of the brain, it has been reasoned, are much too elaborate and complicated in their design and too delicate and precise in their functional adaptation to be constructed by developmental forces alone without aid of functional adjustment. Hypotheses have been formulated along various lines in an attempt to account for the manner in which the neural patterns might become organized through experience. According to one proposal, the neural pathways were supposed to be laid down at first in a diffuse, equipotential manner. Subsequent activity was then presumed to channel out certain adaptive routes in the matrix making these prepotent over the less adaptive pathways. Another interpretation held that synaptic formation itself is constantly influenced by the functional adaptiveness of the completed circuits. Those synapses forming circuits which happen to have adaptive value are somehow reinforced in the growth pro-

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cess whereas those which happen not to be adaptive are resorbed, or atrophy and degenerate. Perhaps the most widely circulated hypothesis has been that of "neurobiotaxis." In this theory it is assumed that the direction of growth and termination of the developing nerve fibers are influenced by electrical potentials generated in neighboring fiber tracts and nuclei during activity. Associations are supposed to be established between tracts and nuclei which happen, in the course of experience, to be activated simultaneously or in close succession.

In contradiction to the viewpoint that function is primary, experiments we have been conducting in recent years on the patterning of synaptic linkages (Sperry, 1941-1950) have consistently supported the opposing contention that the basic integrative plan of the nervous system is organized by developmental forces *per se*. The results leave no doubt that the growth process itself is entirely capable of laying down highly refined integrative patterns, quite independently of functional adaptation. The data, furthermore, are beginning to furnish some insight into the nature and general plan of the developmental forces responsible for this inherent patterning of the integrative pathways.

Before discussing these experiments, it may be well to point out that anyone wishing to study the formation and patterning of synaptic connections is pretty well restricted in the type of experimental material that can be used. There are certain advantages to working with the *regeneration* of synaptic connections in the developed organism. All the evidence so far indicates that the factors responsible for synaptic patterning in regeneration are essentially the same as those operative in initial development. However, the capacity of the developed nervous system to regenerate central synaptic relations appears to be limited for practical purposes to the amphibians and lower vertebrates. Study of the *initial development* of synaptic endings in ontogeny, on the other hand, is likewise most easily conducted in the amphibians where the embryo is readily accessible from the beginning and where the behavioral effects can be determined in early larval stages. As with other phases of experimental embryology, therefore, most of our information has come from the amphibians, i.e., from the frogs, toads, newts, and salamanders.

The nature of the experimental evidence and its implications may best be illustrated, perhaps, by a brief consideration of some of the investigations dealing with the patterning of synaptic connections in the visual pathways. You recall that the fibers connecting the eye and brain have their cell bodies located in the ganglion cell layer of the retina. During development optic axons grow centripetally in the optic nerve to terminate mainly, in the amphibians, in the optic tectum of the mesencephalon. The central connections of the optic fibers must match and reflect the spatial interrelations of all the retinal points from which the fibers arise. This is necessary for accurate visual perception of the direction and speed of movement and for the perception of spatial relationships. Functionally, each retinal point must acquire its own spatial "sign."

It is conceivable that the required pattern of central connections might be attained in development through an orderly timing of fiber ingrowth with mere mechanical guidance of the individual axons. For example, might not the nerve be built in successive concentric layers? The various possibilities of this sort are easily tested by determining the functional effects of optic nerve regeneration in which there is involved a complete disruption of any order in the timing and spatial arrangement of fiber ingrowth. In answer to our question, it has been found that optic nerve regeneration in adult frogs, toads, newts, salamanders, and various species of fishes consistently leads to an orderly recovery of the normal perception of movement and spatial relations. Histological checks have shown that this occurs despite a haphazard disorganization of fibers in the nerve scar. On the basis of such results it has been possible to eliminate mechanical guidance and timing of fiber ingrowth as the responsible organizing factors.

Another way in which the proper pat-

terning of central connections might conceivably be achieved is through functional adjustment. Function could operate in regeneration as well as in initial development through some mechanism such as neurobiotaxis, trial and error channelling, or selective synaptic reinforcement as mentioned above. Possibilities along these lines have been tested by combining transection and regeneration of the optic nerve with 180 degree rotation of the eyeball. Rotation of the eye alone, leaving the nerve connections intact, have been found to cause a reversal and misdirection of visual responses that persists indefinitely in these lower vertebrates without correction by reeducation. When eye rotation is combined with optic nerve section, we find that the visual responses recovered after regeneration are systematically reversed in exactly the same way.

If only one axis of the retina is inverted, as after contralateral transplantation of the eye, the recovered visual responses are correspondingly misdirected with reference only to whichever axis of the eye has been reversed. When this is done in adult newts and salamanders, the retina of the transplanted eye undergoes degeneration and a new retina and optic nerve are regenerated. Nevertheless, functional recovery is the same.

In another type of experiment, the optic nerve of one eye has been cross-united with the contralateral nerve so that the regenerating fibers hook up with the wrong side of the brain. After recovery, such animals respond as if everything seen with one eye were being viewed through the contralateral eye. Under these conditions and in all the foregoing, the various retinal points retain their particular central associations within the optic tectum in a systematic, predetermined manner, despite the intermingling of fibers on their way into the brain and despite the adverse functional effects produced by surgical rearrangement of the normal relations between center and periphery.

A restoration of maladaptive functions can hardly be ascribed to learning or to other forms of functional adaptation. Hence, functional adjustment may be discarded along with mechanical guidance and orderly timing of fiber ingrowth as possible explanations of the patterning of central synapses. Comparison of the scotomata produced by lesions in the optic tectum in normal animals with those produced after optic nerve regeneration indicates an orderly restoration of retinal projection in the anatomical as well as functional sense.

From this and similar evidence we have been able to draw the following tentative conclusions: The fibers of the optic nerve must differ from one another in their constitutional (presumably chemical) properties. This fiber specificity, furthermore, must follow an orderly plan in that it must reflect the topography of the retinal field, each fiber being specified according to the particular locus of the retinal field from which it arises. In order that each retinal locus may have its unique properties, the retinal field must undergo differentation with refer ence to at least two different axes, e.g., anteroposterior and dorsoventral. There probably is additional differentation along the mediolateral axis as well .Were the optic fibers all alike, there would be no means, following their mix-up in the nerve scar, by which they could be distinguished from one another in the centers and their differential functional relations restored.

We have suggested that this fiber specificity probably arises through a polarized differentiation of the retina or its anlage in development, the specificity then being extended from the retinal ganglion cells into their axonal prolongations. Accordingly, it was predicted that if retinal inversion were to be performed sufficiently early, i.e., before polarization had been rigidly determined, normal instead of reversed vision should follow. The possibility was also pointed out that the anteroposterior and dorsoventral axes of the retina may be determined at different stages of development, as in the limb bud, in which case contralateral transplantation of the eye anlage might be expected to produce inverted vision at earlier stages following anteroposterior inversion, for example, than after dorsoventral inversion. Follow-up study of

some of these embryological aspects of inverted vision (Stone, 1944, 1948) appear to be confirmatory as far as they have gone.

It has been possible to deduce further that the second-order tectal neurons with which the optic fibers make synapsis are likewise subject to a refined specification that is correlated with the topography of the optic tectum. Again, if the central neurons were all alike, there would be no means by which the proper patterning of central synapses could be controlled. The tectal specification is presumed to arise through central self-differentiation of the optic lobe.

Finally, since the adjustment of the central relations must be determined with reference to these neuronal specificities, it follows that the formation of synaptic connections must be regulated on some sort of chemo-affinity basis. We may picture the optic fibers, as they invade the optic lobe, encountering many different elements: capillaries, glia cells, axons of other afferents, and the numerous dendrites and cell bodies of the tectal neurons. Not all contacts made by the growing fiber tips result in the formation of synaptic endings. In most cases the growing tips continue to push on beyond the various elements they encounter. It is only when a fiber happens to contact a nerve dendrite or soma, the chemical constitution of which specificially matches that of the invading fiber, that a specialized synaptic ending is formed and further growth of that fiber tip ceases. For each retinal locus we assume a corresponding focal area in the optic lobe. Fibers arising from a given point of the retina have a predetermined, selective affinity for the neurons of the corresponding central locus.

Thus, we conclude that the central reflex relations of the optic nerve, instead of being patterned by electrical or other effects of function, or through a scheduled timing for fiber ingrowth and stereotropic guidance, are determined rather on the basis of interneuronal affinities and incompatibilities of a chemical or physico-chemical nature. These latter are products primarily of embryonic cell differentation and for the most part arise independently of function. With certain qualifications and additions, our conclusions fall within the framework of the old ideas of Cajal (1929), Tello (1923), and others on neurotropism and chemotaxis which, along with those on galvanotaxis, have generally lost prestige in recent decades owing to emphasis on stereotropic factors in nerve growth.

In the visual system the sensory ganglion cells lie embedded within the end-organ itself. In other cranial and spinal nerves the cell bodies of the sensory neurons are located within separate ganglia, only the tips of the sensory fibers being in direct contact with the end-organ tissue. The specification of the sensory fibers, therefore, must typically be achieved on a somewhat different and more complicated plan than that observed in the visual system. The more typical conditions are illustrated in the development of cutaneous local sign.

It is a common capacity of the vertebrates to be able to localize with considerable accuracy and without aid of vision a cutaneous stimulus, like a pinprick, occurring anywhere on the body. Even fish are capable of some localization of this kind. The common catfish is said to localize taste as well as tactile stimuli over the entire body surface. There is something about the excitations entering the brain from different points on the cutaneous covering that indicates the locus from which the excitations arise. This is known as the "local sign" quality of cutaneous sensibility.

These local sign properties depend upon the central connections of the cutaneous fibers. This is clearly demonstrated by the false reference of sensations that follows misregeneration of cutaneous fibers into foreign regions of the integument. For accurate localization, it is necessary that the peripheral connections of the cutaneous neurons match perfectly the central connections with reference to the topography of the entire body surface.

We have been interested in recent years in the problem of how this neat adjustment between periphery and centers is brought about in development. The localizing responses of the frogs and

newts have been found to be sufficiently developed to serve as criteria for study of the ontogeny of cutaneous local sign. As in the visual system, it has been possible to demonstrate that the central connections are not patterned on the basis of an orderly plan in the timing and mechanical guidance of sensory fiber ingrowth. Normal reflex patterns are systematically restored in centripetal regeneration of the sensory roots (Sperry and Miner, 1949; Sperry, 1950a.) This is the case even when the regenerating fibers have been forced to enter the brain over the pathways of a foreign nerve root.

It has been possible to show also that, in the amphibians at least, the central synapses are not patterned through processes of functional adaptation. For example, after contralateral cross-union of the ophthalmic nerves in frog tadpoles, the metamorphosed frogs consistently wipe off the right side of the snout when the left side is stimulated. After transplantation of skin flaps across the midline of the back in frog tadpoles, the metamorphosed frogs continue to wipe erroneously at the original site of the skin flap using the leg on the opposite side of the body. After cross-union of ophthalmic and mandibular nerves in newts, the recovered withdrawal responses to stimulation of the mandible are reversed pressing the skin against the stimulating object instead of pulling it away. After contralateral cross-union of the dorsal nerve roots of the hind limb in frog tadpoles, the metamorphosed frogs make characteristic, but useless and maladaptive responses of the left limb instead of the right when the right foot is stimulated.

In all these cases the central synaptic connections are formed in predetermined fashion according to the usual systematic plan. The synaptic patterning cannot be attributed to functional adaptation in these instances, however, because the various surgical rearrangements have rendered the synaptic patterns maladaptive. Although it has been commonly thought that cutaneous local sign in the higher vertebrates is something that is acquired by experience, there is contradicting evidence (Sperry, 1943a; 1945c) indicating that in the mammals as well and even in man it is based upon an inherent organization patterned through developmental forces.

It has been necessary to conclude that there exists a chemical specificity among the sensory cutaneous neurons which parallels closely their functional differentiation. Specification of the central neurons also has been a necessary inference. The patterning of reflex associations, therefore, seems to be regulated in the cutaneous, as in the visual, system by selective chemoaffinities between the central and peripheral nerve cells.

There remains the problem of the adjustment of the peripheral connections in the skin and how these are made to match correctly the specific properties of the sensory neurons and thereby their central connections. In order to explain this, we have to infer that the integument itself is subject to an extremely refined local specification. Each cutaneous locus must have its own unique chemical properties. This could be attained through a graded, field-like specification of the integument, without necessitating any mosaic or punctiform type of specificity.

Assuming this specification of the integument, it becomes possible to account for the adjustment of the peripheral connections. One might postulate, for example, a selective outgrowth of the different fiber types, each to its appropriate cutaneous locus. This possibility, however, has been contradicted by the evidence in favor of an alternative. The actual data (Miner, 1950) indicate that the cutaneous fibers grow out and connect with the integument largely at random within the body segments, after which the differentiation of the integument induces a corresponding specificity in the attached nerve fibers according to the locations of their cutaneous contacts. Thoracic nerves that normally innervate the skin of the back and trunk of the frog can be forced, by limb-bud transplantation and other means, to grow into and innervate limb skin. Under these conditions the *thoracic* nerves will establish central reflex relations appropriate for the peripheral *limb* connections. Instead

of the typical responses aimed at the back or trunk, stimulation of such thoracic fibers elicits responses characteristic of limb stimulation.

The experiments so far have shown that the developing cutaneous nerves will readily innervate atypical cutaneous areas, and that the type of central reflex relations which are formed depends upon the type of integument with which the nerves connect in the periphery. When we put together the foregoing findings, we can begin to account for the way in which each cutaneous point manages to acquire its proper "local sign" and how the overall map of the body surface gets projected, so to speak, into the central circuits without aid of functional adjustment.

In addition, the cutaneous circuits must necessarily be neatly integrated with the mechanisms mediating kinesthesis and posture sense. A given cutaneous point on the back of the hand in man, for example, may be perceived at any one of almost an infinite number of points in space depending upon the posture of the arm at the time. Retinal local sign is subject to the same complication. Although somewhat simplified, similar integration is present in the frog. Responses elicited from a given cutaneous point vary also with reference to other factors. For example, withdrawal reactions in a frightened animal may undergo a complete reversal to become positive approach responses if the animal is no longer frightened, but is hungry.

In our discussion of the development of the visual and cutaneous pathways, several features have been illustrated which appear to have rather wide applicability for the establishment of central-peripheral relationships, in general. The refined, local differentiation of the endorgan tissues, and the correlated neuronal specification through endorgan contacts were first demonstrated for the limb musculature and its innervation (Weiss, 1936; 1941). They have since been reported for the extrinsic musculature of the eye and the endorgans of the labyrinth, as well as for the retina and integument. We now believe the same holds true for all other organs and tissues in which local sign sensibility or differential motor function is present, for example, the tendons, joints, fascias, periosteum, and the various viscera.

Along with the foregoing, the influence of the peripheral associations upon the patterning of central synapses, as illustrated in the visual and cutaneous pathways, appears to be a general principle in neurogenesis. We have referred to this as the "peripheral regulation of central synapsis."

In general, the differentiation and refined specification of the endorgan tissue leads the way in development. Specification is then secondarily induced in the nerve fibers by the endorgan contacts they happen to form. In this way the differentiation of the periphery becomes projected along the peripheral nerves into the centers and thereby the proper central hook-ups with the peripheral endings is made possible.

Another point illustrated in the examples, is the central self-differentiation of the second and higher-order neurons within the central nuclei. The neurons of the primary sensory nuclei appear to undergo differentiation, in some cases, according to the anatomical relations and dimensions of the nuclear structure itself, as in the optic tectum. In other cases, the central neurons are more scattered and presumably their specification is more dependent upon their efferent associations.

The two types of neuronal specification mentioned above, i.e., intrinsic self-differentiation, on the one hand, and that attained through contact with other cells by extrinsic inductive actions, on the other, are not as distinctly separable as might be inferred from our abbreviated discussion. The final specificity of many neurons must depend upon the summated result of both processes. For example, the primary cutaneous neurons presumably undergo a certain amount of self-differentiation prior to and independently of the peripheral effects. A rostro-caudal differentiation of the sensory ganglia along the neuraxis probably precedes any peripheral contacts. The modal differentiation into pain, tactile and thermal neurons also may be independent of the peripheral contacts. Local specificity we

view as a late refinement superimposed upon these grosser differentiations.

The preceding statements concerning random outgrowth of peripheral nerves are, likewise, subject to some qualification. Peripheral nerve outgrowth is by no means entirely fortuitous. Selectivity is imposed in a varying degree by the mechanical restrictions of nerve outgrowth and also by the modal characteristics of the various neuron types. Outgrowth and termination appear to be selective at least to the extent of preventing mix-ups, for example, between motor and sensory fibers, or between cold, tactile, proprioceptive, and taste fibers, etc.

Thus far we have dealt primarily with the adjustment of peripheral connections and of synaptic associations in the primary motor and primary sensory nuclei. You may ask whether the same principles apply at all to the patterning of synaptic relations in the more central portions of the integrative circuits, i.e., in the secondary and tertiary nuclei and in the various higher association centers of the brain. What evidence we have thus far indicates that this is the case. Experiments involving regeneration of the long intracentral association tracts linking the midbrain, diencephalon, and forebrain with the lower centers of medulla and cord have yielded results consistent with those above. We find that the formation of these intracentral synaptic associations takes place in the usual orderly fashion despite mechanical intermixing of the fibers and despite resultant maladaptiveness in function.

The evidence would seem now to be sufficiently extensive to warrant the conclusion that the developmental patterning of synaptic linkages is regulated on these same principles throughout the nervous system. If we put together the experimental evidence now available regarding the patterning of neuronal connections for the primary sensory, the primary motor, and the intracentral neurons, it becomes possible to draw up a working picture of the development of the complete reflex pathway. This we are now able to do for the optokinetic reflexes, the vestibulo-ocular reflexes, the myotatic (tendon, or muscle-stretch) reflexes, and some of the cutaneous reflexes.

In summary, it appears that the nervous system during development undergoes a refined differentiation or specification in which the individual neurons gradually acquire specific constitutional properties. This is achieved in part by intrinsic self-differentiation, particularly within the centers, and in part by inductive effects imposed through distant fiber contacts. As the elongating processes of the developing neurons begin to invade and to ramify within the neighboring and distant synaptic regions of the neuraxis, the formation of synaptic linkages does not, even at the beginning, proceed in any promiscuous fortuitous, or equipotential fashion. Synaptic association is not established between any and all neurons that happen to make contact. Only when a nerve fiber encounters another neuron the chemical properties of which are specifically suited to those of the growing fiber, does establishment of the intimate and lasting synaptic union result.

The fact that the distribution of neuronal specificities in the growing embryo and the resultant patterns of synaptic linkage turn out to be functionally adaptive for the organism is explainable, like other organ adaptations, in terms of evolutionary selection. Our attempts to analyze the direct mechanisms by which this adaptive patterning is assured in the developmental process itself, have been applied thus far only to some of the simpler sensory-neuro-motor relations.

The question always arises: To what extent are our findings in the lower vertebrates applicable to the higher mammals, including man? In general, we can only answer that the embryonic processes are known to show greater constancy in evolution than do adult characteristics. We have no reason to suppose that any radical revolution has occurred in phylogeny in the methods and principles used in assembling the basic integrative architecture of the vertebrate nervous system. That there has been considerable refinement and alteration in the details of their application, on the other hand, is to be expected. In particular, the part played by learning in patterning the

neural circuits increases tremendously in the higher primates and man. Insofar as we can tell at present, this change seems to be a matter, not so much of substituting learned circuits where inherent circuits previously prevailed, as of adding new brain structures for regulation of the more primitive circuits and final common pathways. These new additions, in which the organization is dependent to a much greater extent upon function and the learning process, seem in large part to be superimposed upon the older integrative mechanisms. However, even in man all the complicated interconnections of the nervous system including those of the cerebral cortex, now known to neuroanatomy, insofar as they are typical of the species, must be regarded as products of developmental forces such as those we have been discussing. Any patterning produced by the learning process has yet to be demonstrated anatomically.

Brief consideration of the problems of neural development will reveal that so far we have only begun to scratch the surface. There remains a tremendous amount of detail yet to be filled in before we shall have anything like a complete analysis of the developmental organization of even the simpler polysynaptic reflex pathways.

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CLINICAL APPLICATION OF PENICILLIN AND BACITRACIN VAGINAL SUPPOSITORIES*

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The ever-changing status of the vagina and cervix brought about by adolescence, menstruation, copulation, pregnancy, parturition, and menopause makes them extremely vulnerable to invasion by microorganisms capable of causing a variety of local infections which not infrequently become systemic in character. With the introduction of local means of therapy, no effort has been spared in seeking suitable local agents to combat vaginal infections or in clearing the vaginal tract of its pathogenic organisms. Soap, iodine, mercurial, arsenical, silver, acid, alkaline and alcoholic preparations are still being employed with variable success. Numerous powders, suppositories, jellies and solutions have been introduced with the aim of bringing about a normal vaginal pH, thus aiding the vagina in ridding itself of the offending organisms. Recently the sulfonamides have been introduced for local vaginal therapy with some beneficial results.

Because of the relatively high morbidity rate encountered by us in vaginal hysterectomies, and because it was believed that morbidities were primarily caused by pathogenic bacteria which could not be eliminated from the vagina and cervix by most careful cleansing prior to operation with the aforementioned agents, a suitable vaginal antibacterial agent was sought. The introduction of penicillin vaginal suppositories for the treatment of acute vaginitis by Lovelady and his associates[1] prompted the employment of the same suppository, prophylactically, prior to vaginal operations.

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Results with Penicillin Suppositories

The first study dealt with the effect of penicillin vaginal suppositories on morbidity in vaginal hysterectomies and on the vaginl flora[2]. The results were most gratifying. By merely inserting a 100,000 unit penicillin cocoa butter suppository vaginally 12-14 hours prior to operation, the morbidity in 100 consecutive vaginal hysterectomies was 7 per cent. This compared most favorably with 37.5% morbidity in the senior author's 56 cases prior to the use of the suppository, with a morbidity of 34.8% in a control series of 210 cases, and with the reported morbidity in the literature which varied from 26 to 42 per cent. Vaginal culture studies taken before and 12 to 14 hours after the insertion of a suppository revealed almost complete elimination of the pyogenic cocci, a 50% reduction in the *Enterobacteriaceae* and no effect on the yeasts.

Results with Bacitracin Suppositories

A study employing a suppository containing 10,000 units of bacitracin was undertaken. The results were comparable to that of the penicillin series[3].

The management of chronic cervicitis and cervical erosion is an extremely tedious process. In many instances it takes months of treatment to accomplish the desired result.

Fifty-nine patients were given a bacitracin suppository twice daily for 7 days following electro-cautery for chronic cervicitis or cervical erosion. They were observed weekly for a period of 4 to 8 weeks. Thirty-nine had complete epithelialization within 14 days, nine had complete healing at the end of three weeks and eleven had to be recauterized and were given a repeat course of bacitracin suppositories. Nine of the latter group cleared up at the end of the eighth week and only two are not yet healed. To date there were no untoward reactions observed from prolonged use of bacitracin suppositories.

Results with Penicillin-Bacitracin Suppositories

In view of the findings that some vaginal organisms were found to be resistant to either bacitracin or penicillin and none were found resistant to both[3], a suppository containing 100,000 units of penicillin and 10,000 units of bacitracin was introduced vaginally 12-14 hours prior to operation in 29 patients undergoing gynecological operations. Two had simple vaginal hysterectomies, two had vaginal plastics alone, and eighteen had hysterectomies with vaginal plastics and/or removal of one or both adnexae. Only one patient had a temperature elevation up to 101.4° F. which lasted for 3 days and was controlled with parenteral penicillin for 4 days. The morbidity in this series was 4.5%.

Seven patients had abdominal hysterectomies with 3 cases of morbidity. However, these patients had associated intra-abdominal pathology which no doubt caused the morbidity.

Comment

It is hardly necessary to re-emphasize that bacitracin or penicillin vaginal suppositories are of great value preparatory to total hysterectomy or any kind of vaginal operation. The clinical and bacteriologic results speak for themselves. A vaginal flora free of potential pathogens, which these antibiotic suppositories seem to establish, should be a prerequisite for any vaginal operation.

During the past year other gynecologists employing penicillin suppositories corroborated our results. Allen[4] was able to reduce his personal morbidity in vaginal hysterectomy from 17 to 8 per cent. Kanter[5] in a series of 100 cases performed by the gynecologic staff at the Presbyterian Hospital, Chicago, reported a morbidity of 12 per cent. De Costa[6] from the Michael Reese Hospital also reported favorable results. Fletcher[7], working independently, but using many more penicillin suppositories, reported a reduction of his morbidity from 37.5% to 7.2%.

Conclusion

1. Bacitracin and penicillin suppositories are of value when employed vaginally prior to total hysterectomy or any vaginal operation.

2. The combination of penicillin and bacitracin into one suppository for prophylactic use appears to be of value since many more organisms can be eliminated by the synergistic effect and by the chance that the bacteria will not remain resistant to both antibiotics.

3. Bacitracin suppositories were found to be an aid in the management of chronic cervicitis and cervical erosion following electro-cautery.

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5. Kanter, Aaron E., Discussion of Turner, Ref. 2.
6. De Costa, Edwin, Discussion of Turner, Ref. 2.
7. Fletcher, P. F., *South. M. J., 43*:715, Aug. 1950.

Editor's Note:

Articles in The Chicago Medical School *Quarterly* are now being abstracted in the following journals: *Excerpta Medica, Chemical Abstracts,* and *Biological Abstracts.*

BOOK REVIEWS

PRACTICAL GYNECOLOGY, by Walter Reich, M.D., F.A.C.S., F.I.C.S., Assistant Professor of Gynecology, The Chicago Medical School, and Mitchell J. Nechtow, Associate in Gynecology and Obstetrics, The Chicago Medical School. First edition. Cloth. 449 pages. Philadelphia: J. B. Lippincott Co., 1950. $ 10.00.

For some time, a need has been felt for a work which would stress the clinical aspects of gynecology. This book fills the need admirably. The contents are based on the personal observations of the authors at Cook County Hospital, as well as in their private practices.

The method of presentation is lucid and readable. The role of the history in gynecologic diagnosis is stressed — and rightly so. The techniques of the various parts of the physical examination are gone over in detail. A special section entitled, "Examination of the Breasts," is also included. This corrects a hiatus which has long existed in gynecologic texts. Laboratory examinations, including biopsy and the Papanicolau staining techniques, are discussed and the methods used for the withdrawal and preservation of the specimens are explained. The various disease complexes are discussed in a systematical order and a special section is devoted to the psychosomatic approach to the sexual problem. The last chapter is an excellent discussion of the place the physician should take in a pre-marital examination and in pre-marital counseling. The final section is composed of 34 color plates which help diagnose common gynecologic abnormalities.

This book is highly recommended for all junior and senior medical students as well as for all practitioners.

A PRIMER FOR DIABETIC PATIENTS. By Russell M. Wilder, M.D. Cloth. Ninth edition. 181 pages with 9 illustrations. Philadelphia and London: W. B. Saunders Company, 1950. $2.25.

It has been said that the life expectancy of a diabetic varies with his knowledge of the disease. The "Primer" as a source of such information is current, clear, practical and simple. It is highly recommended to the diabetic patient and to the physician in their co-operative effort to maintain the patient's health.

AN ATLAS OF HUMAN ANATOMY. By Barry J. Anson, Ph.D. Cloth. 504 pages with 1301 illustrations. Philadelphia and London: W. B. Saunders Company, 1950. $11.50.

The field of human anatomy has been enriched by the addition of this beautiful atlas. The drawings by various well known medical illustrators are certain to be well received by both students and teachers of anatomy. They are clear, complete and accurate though simple, esthetically appealing and free of confusing detail. Anatomic variations are given for certain of the structures; these are of particular value to the surgeon. It is recommended that future editions make more liberal use of color. The text is held to a minimum, serving the proper function of merely amplifying the picture. The book is highly recommended to students, surgeons and practitioners.

THORACIC SURGERY. By Richard H. Sweet, M.D. Cloth. 334 pages with 155 illustrations by Jorge Rodriguez Arroyo, M.D. Philadelphia and London: W. B. Saunders Company, 1950. $10.00.

Dr. Sweet's book is a masterpiece in its field. Beginning with an excellent section on the surgical anatomy of the thorax, and following this with a generally useful chapter on general technical considerations, the author then discusses clearly and in detail the various surgical procedures. These are arranged anatomically and include sections on cardiac surgery and abdominal surgery by thoracic approach. The book is liberally illustrated with drawings of exceptional clarity by Dr. Arroyo, based on sketches from actual dissections and operations. The book is enthusiastically recommended to surgeons and students of surgery.

PLASTIC AND RECONSTRUCTIVE SURGERY. By Ferris Smith, M.D. 895 pages with 592 figures. Philadelphia and London: W. B. Saunders Company, 1950. $15.00.

Dr. Smith has presented a monumental work in the field of plastic surgery. The book covers the technique and principles of reconstructive surgery, based on current trends and the author's own extensive experience. The book is richly illustrated with over 1000 illustrations in the 592 figures. These demonstrate surgical problems, the technique of the repair, and results. There is included a section on general surgical procedures of value to all practitioners, as well as specialized sections of interest to the oral surgeon, the orthopedic surgeon, the oto-laryngologist, the ophthalmologist, and of course the general surgeon. The book is most highly recommended to all practicing surgeons and students of surgery.

WORLD SURGERY 1950. Edited by Stephen A. Zieman, M.D. Cloth. 177 pages with 53 illustrations. Philadelphia, London, Montreal: J. B. Lippincott Company, 1950. $6.00.

This volume surveys the progress in the field of surgery through a review of the world literature. It is the intention of the editor to acquaint

the surgeon with the advances in theory and practice brought forth by other surgeons throughout the world. Dr. Zieman has been succinct as well as comprehensive in this intent. The book will be found valuable as a reference to all students and clinicians, and is especially recommended to those working in surgery and the subspecialties.

ESSENTIALS OF OPHTHALMOLOGY. By Roland I. Pritikin, M.D. Cloth. 561 pages with 215 illustrations. Philadelphia, London, Montreal: J. B. Lippincott Company, 1950. $7.50.

Written for the non-specialist, this volume presents the entire field of ophthalmology in a concise and practical fashion. Broad and basic principles are stressed. The book is divided into two parts. The first deals with anatomy, physiology, examination and refraction of the eyes, including a section on industrial ophthalmology. Part two deals with eye diseases. The book is well outlined and well illustrated. It will be found useful to the medical student and to the practitioner both for study and for reference.

THE MASK OF SANITY. By Hervey Cleckley, M.D. Cloth. Second edition. 569 pages. St. Louis: C. V. Mosby Company, 1950. $6.50.

The second edition further elaborates upon the prime purpose of this work, the description of the psychopathic personality and the psychopathic patient. Dr. Cleckley has made an exhaustive study of the field which results he reports in the only book of its kind. The book reads easily and is for the most part nontechnical. The cases reported demonstrate the protean manifestations of the psychopathic prototype. The book is recommended to the interested reader in both the lay and medical fields.

NUTRITION IN HEALTH AND DISEASE. By Lenra F. Cooper, M. H. E., Edith M. Barber, M. S., Helen S. Mitchell, M. S., and associate author Henderika J. Rynbergen, M. S. Cloth. 11th edition. 688 pages with 133 illustrations. Philadelphia, London, Montreal: J. B. Lippincott Company, 1950. $4.00.

Intended for the practical nurse, this book combines the principles and the practice of dietetics. It has been written in a manner also suitable for the lay reader. Menus and recipes are presented for diet planning of infants, children, adults, the aged, the family as a whole and for various illnesses. The book is highly recommended to the practical nurse and dietitian, as well as to the housewife. The physician will find the book useful in prescribing diets to all types of patients.

PARS PRO TOTO. By Alfred Peyser. Cloth. 196 pages. Stockholm: Almquist and Wiksell, 1950.

The function of this little book is explained in its subtitle: "Abbreviations in international medical literature including sister sciences in six languages." These include English, German, French, Spanish, Italian and Swedish. The book will be found useful to those doing research in the medical literature, and should be in all medical libraries.

SCHOOL NOTES

FACULTY NEWS

It is with pride that we welcome Dr. Roscoe C. Giles, Assistant Professor of Surgery, to The Chicago Medical School. He received his medical degree at Cornell University, College of Medicine in 1915. He interned at Provident Hospital, Chicago, and has been Senior Attending Surgeon there since 1925. He took leave of absence from Provident Hospital in 1930 to accept a fellowship from the General Education Board and the Julius Rosenwald Fund to go to Vienna for a period of eighteen months. Upon his return, he accepted a fellowship in Bone Pathology at the University of Chicago. Since 1938, Dr. Giles has been a Diplomate of the American Board of Surgery and in 1945, Dr. Giles was elected a Fellow of the American College of Surgeons. He is also a member of the American Medical Association and is a Founder-Fellow of the International College of Surgeons. In 1947, Dr. Giles was appointed Alternate Attending Surgeon at the Cook County Hospital.

Dr. Giles has contributed extensively to medical literature and is listed in "Who's Who in Medicine in Illinois"; "Who's Who in Medicine in America"; and "Who's Who in Medicine in the World". He has served as president of the John A. Andrew Clinical Society, Tuskegee, Alabama (1928) and of the National Medical Association (1936).

We would like to take this opportunity to welcome Dr. Phillip Shubik to the staff as Coordinator of the Cancer Teaching and Research Programs and as Assistant Professor of Surgery at The Chicago Medical School.

Dr. Shubik was born in London in 1921. He attended Oxford University where he received his Bachelor of Arts degree in 1940. He continued his studies at Oxford University and in 1943, he received his Doctor of Medicine degree. During the next year he served as Interne and Junior Resident in the various hospitals in London as was the practice during the war. In 1944, Dr. Shubik was commissioned a Major in the British Army Medical Corps and was sent to India where he was Commander of a base hospital. In 1947, he returned to Oxford to resume his studies in the School of Pathology. During this period he was also Demonstrator in Pathology at the University. Dr. Shubik was awarded his Ph.D. in Pathology in 1949.

That same year he came to the United States and was appointed Instructor in Pathology at Northwestern University. In 1950, he came to The Chicago Medical School.

At the present time Dr. Shubik is engaged in studying the mechanics of skin carcinogenesis. This is a continuation of previous work that he has been doing. He has had his previous papers published in the British Journal of Cancer. Dr. Shubik is a member of the Society of Pathology and Bacteriology of Great Britain, the Society of Experimental Biology and Medicine and the American Association of Cancer Research.

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At the present time, Dr. George J. Scheff is working on two major projects. The first of these is concerned with capillary permeability studies in experimentally induced rheumatic fever-like conditions in rabbits. Such studies seem to be indicated because disturbances of capillary function may be a contributory factor in the development of this disease. These capillary injuries are seemingly brought about by a toxic agent or allergic condition. These investigations are supported by a grant of the Chicago Heart Association.

The second problem deals with the search for the possible existence of a splenic hormone. As test object the Bartonella muris infected rat was chosen. This infection in these animals remains latent unless splenectomy is performed. After splenectomy, a very severe anemia develops and a large number of animals die. Whether or not the absence of the spleen can be counteracted by the administration of splenic extract remains to be proved. If so, this would indicate that the extract contains some ingredient which replaces the extirpated spleen. The expense of this research is defrayed by a grant of Armour & Company.

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Dr. Israel Davidsohn, Professor and Chairman, Department of Pathology of The Chicago Medical School, and Director of Laboratories and Pathology, Mount Sinai Hospital, has been elected President-Elect of the American Society of Clinical Pathologists for 1950-51.

NEW FACULTY APPOINTMENTS

Department of Medicine

Assistants in Medicine: Dr. Harold R. Kamenear, Dr. Herbert H. Krantz, Dr. Harry B. Lerner, Dr. Daniel L. Streicher, Dr. Samuel Solomon, Jr.

Department of Neurology and Psychiatry

Associate in Neurology: Dr. Louis Berlin, Dr. Bernard Skorodin.

Instructor in Psychiatry: Dr. Charles F. Samelson, Dr. Harold Klehr.

Department of Pediatrics

Instructor in Pediatrics: Dr. Gordon Cherwitz.

Assistant in Pediatrics: Dr. Hyman S. Gordon, Dr. Jack W. Gaines.

Department of Physiology and Pharmacology

Instructor in Pharmacology: Dr. Russell O. Hanson.

Faculty Promotions:

Dr. David Cohen — Professor of Dermatology.

Dr. Donald H. Atlas—Associate Professor of Medicine.

Dr. Irving Siegel—Associate Professor of Obstetrics.

Dr. Kurt Stern—Assistant Professor of Pathology.

Dr. Morris Goldenberg—Assistant Professor of Pathology.

Dr. Paul H. Kopper—Assistant Professor of Microbiology and Public Health.

Dr. David B. Radner—Assistant Professor of Medicine.

Dr. Meyer J. Steinberg—Assistant Professor of Medicine.

The Faculty and Alumni Association extend their heartfelt sympathy to the families and friends of these honored dead:

Dr. Frank F. Smejkal — Associate Professor of Medicine.

Class of 1899 — Dr. Peter J. Latz of Chicago, Illinois.

Class of 1922 — Dr. Paul E. Thal of Zion, Illinois.

Class of 1933 — Dr. George H. Flickinger of Hopedale, Illinois.

Class of 1908—Dr. William F. Schaffer of Chicago, Illinois.

A grant in the amount of $3,000 from the White Laboratories of Newark, New Jersey, has been made for use in cardiovascular research. It will be administered by Dr. Aldo A. Luisada, Director of the Program of Cardiology of The Chicago Medical School.

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Arrangements are being made for the second annual Maurice Oppenheim Memorial lectureship which is to be held at Kling Auditorium on January 26th with Doctor Karl Menninger of the famed Menninger Clinic as guest speaker. This lecture is sponsored by the Alpha Rho Chapter of the Phi Lambda Kappa Fraternity.

ALUMNI NEWS

Class of 1950

Congratulations are in order to Dr. and Mrs. Abraham Ludwig on their marriage on September 2, 1950, in Brooklyn, New York.

Best wishes to Dr. and Mrs. Alfred Greenberg on their marriage on June 24, 1950, in Chicago, Illinois.

Congratulations to Dr. and Mrs. Philip Oransky on the birth of a son, Steven Alan on October 9, 1950.

Class of 1947

Congratulations to Dr. and Mrs. Jerome A. Ehrlich on the birth of a son, Richard Smythe, on May 18, 1950.

Dr. Edward R. Svetkey announces the opening of his office for the general practice of Medicine and Surgery in Kenelworth Gardens, Scarsdale, New York.

Class of 1946

Congratulations to Dr. and Mrs. Alan C. Siegel on the birth of a daughter, Paula Wyrene on October 12, 1950.

Dr. Melvin F. Herman announces the opening of his offices in Bayside, Long Island, New York.

Class of 1941

Dr. Arnold S. Block announces the opening of offices for the practice of Psychiatry at 634 North Grand Boulevard, St. Louis, Missouri.

Class of 1940

Congratulations to Dr. and Mrs. Sidney Greenberger on their marriage in Chicago.

Class of 1933

Congratulations to Dr. and Mrs. George Altbach on the birth of a daughter, Gail, on August 11, 1950.

STUDENT NEWS

Class of 1951

Congratulations are in order to David Baker on his being awarded the third year scholarship for the highest academic standing in his class.

Congratulations are extended to the following seniors on their marriages:

Jerry J. Cohen to Miss Ruth Goldstein of Chicago.

Jesse Schessel to Miss Nanette Siegel of Chicago.

Best wishes to Al. Schwartz on his engagement to Miss Gloria Bell.

Best wishes to Perry Gross on his marriage to the former Miss Harriet Bernstein of Waterloo, Iowa, on June 18, 1950.

Congratulations to Larry Berger on his marriage to Miss Beatrice Neuringer.

Best wishes to Mr. and Mrs. Sherwin Lutz on the birth of Karen Tobey on November 18, 1950.

Class of 1952

We wish to take this opportunity to extend our congratulations to Miss Marie Sathmary and Mr. Robert Katz, both of the Class of 1952, on the announcement of their engagement. Mr. Katz and the future Mrs. Katz are both of Brooklyn, New York.

After a long wait, Lloyd Paul has finally decided to take the step and announces his engagement to Miss Doris Siegel of Detroit. Congratulations.

Congratulations to Milton Arnold on his marriage to the former Miss Sylvia Stillerman of Chicago on December 23, 1950.

Best wishes are also extended to Bernard Penner on his marriage to the former Miss Natalia Skud of Chicago which was also on December 23, 1950.

Class of 1953

Contgratulations to Sander Breiner on his engagement to Miss Beatrice Oboler of Chicago.

ASSOCIATION OF INTERNES AND MEDICAL STUDENTS

The Association of Internes and Medical Students continued to lead a very active existence at The Chicago Medical School throughout the entire past quarter. Its first meeting was held only two days after the quarter began and served to introduce the new freshmen class to the organization. Dr. Peter Gaberman, advisor to AIMS, addressed the meeting. He praised the organization's fight for better conditions for internes and medical students and said the popularity of AIMS was the result of its continuing to meet the need of medical students and internes for an independent organization to represent them and express their views.

AIMS inaugurated a series of lectures on important scientific and medical subjects with the appearance of Dr. Lester Dragstedt, world famous surgeon. Dr. Dragstedt spoke on the subject, "The Physiology of the Gastric Secretions and Its Relationship to the Ulcer Problem."

On the lighter side, the CMS and Illinois Chapters jointly sponsored a very successful AIMS "Turkey Gobble" Thanksgiving Dance.

There were several meetings devoted to pre-convention discussions of AIMS policy and delegates were then elected to the National Convention which this year was held at Howard Medical School, Washington, D.C., December 26-29.

STUDENT AMERICAN MEDICAL ASSOCIATION

As a young organization the Chicago Medical School Chapter of S. A. M. A. has been actively expanding its educational program of lectures and motion pictures. Recently Drs. Rosenthal, Bettag, Levine, and Newitt, all of whom are prominent in the field of tuberculosis control, engaged in a lively panel discussion on "The Efficacy of B. C. G." On November 29, 1950, Dr. Oliver Field, Director of the Bureau of Investigation of the A.M.A., presented a lecture on "Quackery, Medical Fads and Fakes."

Representatives from twenty-five medical schools are expected to attend a convention launching the national organization. This first annual convention is to be held in Chicago during the Christmas interim. A national constitution will be written and plans for the future role of this organization are to be formulated.

At a recent election, Jerry Gold was elected president and will represent the chapter at the convention. Walter Griesbach is vice-president, Norman Bacher is secretary, and Donald Behr is treasurer of the organization.